(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁷: C12N 5/10, 15/12, 15/63, 15/64, C07K 14/47, 14/705, 14/715, G01N 33/53, 33/567

(21) International Application Number: PCT/US00/19094

(22) International Filing Date: 13 July 2000 (13.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/143,435   13 July 1999 (13.07.1999)   US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— With international search report.
— Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DRUG TARGET ISOGENES: POLYMORPHISMS IN THE INTERLEUKIN 4 RECEPTOR ALPHA GENE

(57) Abstract: Polynucleotides comprising one or more of 38 novel single nucleotide polymorphisms in the human Interleukin 4 Receptor Alpha (IL4Rα) gene are described. Compositions and methods for detecting one or more of these polymorphisms are also disclosed. In addition, various genotypes and haplotypes for IL4Rα gene that exist in the population are described.

DRUG TARGET ISOGENES:

POLYMORPHISMS IN THE INTERLEUKIN 4 RECEPTOR ALPHA GENE

RELATED APPLICATIONS

This application is a continuation-in-part of, and claims priority to, U.S. Provisional Application

5   Serial No. 60/143,435 filed July 13, 1999.

FIELD OF THE INVENTION

This invention relates to variation in genes that encode pharmaceutically important proteins. In

particular, this invention provides genetic variants of the human Interleukin 4 Receptor Alpha (IL4Rα)

10   gene and methods for identifying which variant(s) of this gene is/are possessed by an individual.

BACKGROUND OF THE INVENTION

Current methods for identifying pharmaceuticals to treat disease often start by identifying,

cloning, and expressing an important target protein related to the disease. A determination of whether an

15   agonist or antagonist is needed to produce an effect that may benefit a patient with the disease is then

made. Then, vast numbers of compounds are screened against the target protein to find new potential

drugs. The desired outcome of this process is a drug that is specific for the target, thereby reducing the

incidence of the undesired side effects usually caused by a compound's activity at non-intended targets.

What this approach fails to consider, however, is that natural variability exists in any and every

20   population with respect to a particular protein. A target protein currently used to screen drugs typically is

expressed by a gene cloned from an individual who was arbitrarily selected. However, the nucleotide

sequence of a particular gene may vary tremendously among individuals. Subtle alteration(s) in the

primary nucleotide sequence of a gene encoding a target protein may be manifested as significant.

variation in expression of or in the structure and/or function of the protein. Such alterations may explain

25   the relatively high degree of uncertainty inherent in treatment of individuals with drugs whose design is

based upon a single representative example of the target. For example, it is well-established that some

classes of drugs frequently have lower efficacy in some individuals than others, which means such

individuals and their physicians must weigh the possible benefit of a larger dosage against a greater risk

of side effects. In addition, variable information on the biological function or effects of a particular

30   protein may be due to different scientists unknowingly studying different isoforms of the gene encoding

the protein. Thus, information on the type and frequency of genomic variation that exists for

pharmaceutically important proteins would be useful.

The organization of single nucleotide variations (polymorphisms) in the primary sequence of a

gene into one of the limited number of combinations that exist as units of inheritance is termed a

35   haplotype. Each haplotype therefore contains significantly more information than individual unorganized

polymorphisms. Haplotypes provide an accurate measurement of the genomic variation in the two

chromosomes of an individual.

It is well-established that many diseases are associated with specific variations in gene sequences. However while there are examples in which individual polymorphisms act as genetic markers for a particular phenotype, in other cases an individual polymorphism may be found in a variety of genomic backgrounds and therefore shows no definitive coupling between the polymorphism and the causative site

5 for the phenotype (Clark AG et al. 1998 *Am J Hum Genet* 63:595-612; Ulbrecht M et al. 2000 *Am J Respir Crit Care Med* 161: 469-74). In addition, the marker may be predictive in some populations, but not in other populations (Clark AG et al. 1998 *supra*). In these instances, a haplotype will provide a superior genetic marker for the phenotype (Clark AG et al. 1998 *supra*; Ulbrecht M et al. 2000, *supra*; Ruaño G & Stephens JC *Gen Eng News* 19 (21), December 1999).

10 Analysis of the association between each observed haplotype and a particular phenotype permits ranking of each haplotype by its statistical power of prediction for the phenotype. Haplotypes found to be strongly associated with the phenotype can then have that positive association confirmed by alternative methods to minimize false positives. For a gene suspected to be associated with a particular phenotype, if no observed haplotypes for that gene show association with the phenotype of interest, then it may be

15 inferred that variation in the gene has little, if any, involvement with that phenotype (Ruaño & Stephens 1999, *supra*). Thus, information on the observed haplotypes and their frequency of occurrence in various population groups will be useful in a variety of research and clinical applications.

One possible drug target for the treatment of allergies, asthma, and other immune responses is the Interleukin 4 Receptor Alpha (IL4Rα) gene or its encoded product. IL4R is a transmembrane complex

20 composed of two different protein subunits, a 140-kDa high affinity binding subunit named interleukin-4 receptor α (IL-4Rα; also known as CD124 antigen) and either a gamma-c subunit, which is present in several cytokine receptors, or an interleukin-13 receptor 1 (IL-13R1) subunit. Both subunits of the IL-4R are required to bind interleukin-4 (IL-4) and to mediate its transcription-activating effects through the tyrosine kinases, Jak1 and Jak3. Upon binding of IL-4 to the IL-4R, Jak 1 and Jak 3 phosphorylate the IL-

25 4Rα subunit, creating binding sites in the cytoplasmic domain for many other proteins, including SOS, Stat-6, c-fes, and *src* homology phosphatase 1 (SHP-1). Activated Jak proteins also phosphorylate Stat-proteins, which travel into the nucleus and function as transcription factors. Other IL-4 signal pathways exist, but are less well characterized.

IL-4, one of the most important cytokines involved in the allergic response, is produced when

30 cells from the immune system, in particular T cells, are activated in response to an allergen. Regulation of the immune response involves Helper T-cells that differentiate into two subtypes, Th1 and Th2. Th1 cells express interferon-gamma and interluekin-2 (IL-2), and mediate a cell-based immunity, where macrophages and neutrophils are prominently involved. Th1 cells also direct the IgE-producing B cells, as well as mast cells, basophils and eosinophils. Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13.

35 Each Th cell subtype represses the other, so the immune system is forced into differentiation into either a Th1 or Th2 response against an external allergic challenge. In many instances an aberration of this response can render a pathological state such as a Th2 response against ragweed.

IL-4 induces in B cells the synthesis of IgE type antibodies that recognize specific allergens. IgE binds to receptors on mast cells and basophils and mediates the early humoral (sub-chronic) response on the B-side of the immune system. If an allergen binds mast cell-attached IgE, the mast cell releases mediators like histamine, and the eicosanoid leukotrienes and prostaglandins products, some of which

5   cause the familiar symptoms of an acute allergic reaction: swelling, itching, mucous, and reddening of the skin. Later in this process eosinophils and other inflammatory cells migrate to the site of inflammation. This later phase is important in asthma, because the eosinophils may instigate a more chronic inflammation which can adversely scar lung tissue. IL-4 is at least partly responsible for recruiting eosinophils, because it induces synthesis of specific adhesion molecules on the capillary endothelium, and

10   stimulates expression of IL-5 and eotaxin. IL-5 leads to the development of a large number of eosinophils from precursor cells in the bone marrow, and eotaxin stimulates their migration into the lung tissue.

It has been proposed that inhibition of IL-4 activity would disarm the Th2 component of the immune system. This would then allow the immune system to develop a natural tolerance towards

15   common allergens without the full acute response to the challenge. In this way, tolerance may be induced in many patients, similar to what is sometimes achieved with hyposensitization shots for allergy patients. Thus, substances that inhibit IL-4 production and/or its binding to the IL-4 receptor, may improve the therapy of allergies and asthma.

The gene for IL-4Rα has eleven exons encoding an 825 amino acid protein and spans over 24 kb

20   of the short arm of chromosome 16 (16p12.1) (Pritchard et al., *Genomics* 10:801, 1991; GenBank Accession No. AC004525). A reference sequence for IL4R-α gene, which corresponds to the reverse complement of nucleotides 100020-71331 in the GenBank Accession No. AC004525, is shown in Fig. 1 (SEQ ID NO:1). Reference sequences for IL-4Rα mRNA (GenBank Accession No. NM_000418) and the encoded IL4Rα precursor protein (GenBank Accession No. P24394) are shown in Figs. 2 and 3,

25   respectively (SEQ ID NOS:2 and 3). Significant features reported for the IL-4Rα precursor include: a signal peptide located between a.a. 1 and 25; an extracellular domain between a.a. 26 and 232; disulfide bonds between a.a. 34 and 44 and between a.a. 74 and 86; glycosylation sites at amino acids 53, 98, 128, 134, 176, and 209; a transmembrane region between a.a. 233 and 256; and a cytoplasmic domain between a.a. 257 and 825.

30   Recently, several studies have suggested that genetic polymorphisms in the IL4-Rα gene are associated with genetic predisposition to atopy and/or elevated serum IgE. Mitsuyasu et al., reported that polymorphisms at codons 75 and 576 affect IL-4R function (*Nat. Genet.* 19:119-120, 1998). The IL-4Rα allele with isoleucine at amino acid position 75 (Ile75) in the extracellular domain is more responsive to IL-4 than the allele with valine at that position (Val75) and is associated with atopic asthma but not with

35   non-atopic asthma (Mitsuyasu et al., *supra*). Also, the allele with arginine at position 576 (Arg576) in the cytoplasmic domain exhibits higher receptor activity than the glutamine allele (Glu576) due to reduced

binding by the Arg576 allele of a negative regulatory molecule, *src* homology phosphatase 1 (Imani et al., *J. Biol Chem.* 272:7927-7931, 1997). The Arg576 allele has a higher frequency in patients with allergic inflammatory disorders, including atopy (Khurana Hershey et al., *New Eng. J. Med.* 337:1720-1725, 1997). In a recent study, Hershey et al.; (WO 00/34789) reported that the Arg576 allele is significantly

5   associated with asthma. Studies showed that patients who were homozygous for this allele had about a 9-fold higher risk towards asthma and that two copies of Arg576 are associated in an increase in asthma prevalence and severity. Kanemitsu et al. recently reported that the presence of either the Ile75 or Arg576 variant is significantly associated with susceptibility for developing systemic lupus erythematosus (SLE), a Th2-dominant systemic autoimmune disorder (*Arthritis Rheum.* 42:1298-1300). Another variant IL-

10   4Rα allele that is reportedly associated with atopy susceptibility has proline rather than serine at position 503 (Kruse et al., *Immunol.* 96:365-371, 1999). Other IL-4Rα gene polymorphisms leading to amino acid changes in the cytoplasmic domain of the protein product have been identified at codons 400 (E400A), 431 (C431R) and 786 (S786P) (Kruse et al., *supra;* Deichmann et al., *Biochem. Biophys. Res. Commun.* 231:696-697, 1997). A polymorphism of guanine or adenine at a position corresponding to nucleotide

15   55328 in Figure 1 has also been reported as well as a polymorphism of cytosine or thymine at a position corresponding to nucleotide 55430 (Buetow et al., 1999, Nat Genet. 21:323-5).

Because of the potential for polymorphisms in the IL4Rα gene to affect the expression and function of the encoded protein, it would be useful to determine whether additional polymorphisms exist in the IL4Rα gene, as well as how such polymorphisms are combined in different copies of the gene.

20   Such information would be useful for studying the biological function of IL4Rα as well as in identifying drugs targeting this protein for the treatment of disorders related to its abnormal expression or function.

SUMMARY OF THE INVENTION

Accordingly, the inventors herein have discovered 38 novel polymorphic sites in the IL4Rα gene.

25   These polymorphic sites (PS) correspond to the following nucleotide positions in the reverse complement of the indicated GenBank Accession Number: 32884 (PS1), 32903 (PS2), 32961 (PS3), 33135 (PS4), 35763 (PS6), 35770 (PS7), 35817 (PS8), 35905 (PS9), 35944 (PS10), 35958 (PS11), 37330 (PS12), 37473 (PS13), 37586 (PS14), 37591 (PS15), 37604 (PS16), 37644 (PS17), 37678 (PS18), 43446 (PS19), 43703 (PS20), 53008 (PS21), 53099 (PS22), 53153 (PS23), 53456 (PS25), 53507 (PS27), 53513 (PS28),

30   53915 (PS30), 53949 (PS32), 54237 (PS33), 54468 (PS34), 54611 (PS35), 54698 (PS36), 54700 (PS37), 54741 (PS38), 54780 (PS39), 55083 (PS40), 55142 (PS41), 55539 (PS44) and 55758 (PS45) in AC004525. The polymorphisms at these sites are adenine or guanine at PS1, cytosine or thymine at PS2, guanine or thymine at PS3, guanine or cytosine at PS4, cytosine or thymine at PS6, guanine or adenine at PS7, thymine or cytosine at PS8, cytosine or thymine at PS9, cytosine or thymine at PS10, guanine or

35   adenine at PS11, guanine or adenine at PS12, cytosine or thymine at PS13, cytosine or thymine at PS14, guanine or adenine at PS15, adenine or thymine at PS16, cytosine or adenine at PS17, cytosine or

thymine at PS18, guanine or adenine at PS19, thymine or cytosine at PS20, adenine or cytosine at PS21, cytosine or thymine at PS22, thymine or cytosin at PS23, guanine or thymine at PS25, cytosine or thymine at PS27, thymine or cytosine at PS28, cytosine or thymine at PS30, guanine or adenine at PS32, cytosine or thymine at PS33, thymine or guanine at PS34, thymine or cytosine at PS35, thymine or

5   cytosine at PS36, thymine or cytosine at PS37, cytosine or thymine at PS38, cytosine or guanine at PS39, adenine or guanine at PS40, guanine or adenine at PS41, cytosine or thymine at PS44 and guanine or adenine at PS45. In addition, the inventors have determined the identity of the alternative nucleotides present at these sites, as well as at the previously identified sites at nucleotides 35749 (PS5), 53413 (PS24), 53505 (PS26), 53721 (PS29), 53941 (PS31), 55328 (PS42), and 55430 (PS43). It is believed that

10   IL4Rα-encoding polynucleotides containing one or more of the novel polymorphic sites reported herein will be useful in studying the expression and biological function of IL4Rα, as well as in developing drugs targeting this protein. In addition, information on the combinations of polymorphisms in the IL4Rα gene may have diagnostic and forensic applications.

Thus, in one embodiment, the invention provides an isolated polynucleotide comprising a

15   nucleotide sequence which is a polymorphic variant of a reference sequence for the IL4Rα gene or a fragment thereof. The reference sequence comprises SEQ ID NO:1 and the polymorphic variant comprises at least one polymorphism selected from the group consisting of guanine at PS1, thymine at PS2, thymine at PS3, cytosine at PS4, thymine at PS6, adenine at PS7, cytosine at PS8, thymine at PS9, thymine at PS10, adenine at PS11, adenine at PS12, thymine at PS13, thymine at PS14, adenine at PS15,

20   thymine at PS16, adenine at PS17, thymine at PS18, adenine at PS19, cytosine at PS20, cytosine at PS21, thymine at PS22, cytosine at PS23, thymine at PS25, thymine at PS27, cytosine at PS28, thymine at PS30, adenine at PS32, thymine at PS33, guanine at PS34, cytosine at PS35, cytosine at PS36, cytosine at PS37, thymine at PS38, guanine at PS39, guanine at PS40, adenine at PS41, thymine at PS44, and adenine at PS45. In a preferred embodiment, the polymorphic variant comprises one or more additional

25   polymorphisms selected from the group consisting of guanine at PS5, cytosine at PS24, cytosine at PS26, cytosine at PS29, guanine at PS31, adenine at PS42, and thymine at PS43. A particularly preferred polymorphic variant is a naturally-occurring isoform (also referred to herein as an "isogene") of the IL4Rα gene. An IL4Rα isogene of the invention comprises adenine or guanine at PS1, cytosine or thymine at PS2, guanine or thymine at PS3, guanine or cytosine at PS4, cytosine or thymine at PS6,

30   guanine or adenine at PS7, thymine or cytosine at PS8, cytosine or thymine at PS9, cytosine or thymine at PS10, guanine or adenine at PS11, guanine or adenine at PS12, cytosine or thymine at PS13, cytosine or thymine at PS14, guanine or adenine at PS15, adenine or thymine at PS16, cytosine or adenine at PS17, cytosine or thymine at PS18, guanine or adenine at PS19, thymine or cytosine at PS20, adenine or cytosine at PS21, cytosine or thymine at PS22, thymine or cytosine at PS23, guanine or thymine at PS25,

35   cytosine or thymine at PS27, thymine or cytosine at PS28, cytosine or thymine at PS30, guanine or adenine at PS32, cytosine or thymine at PS33, thymine or guanine at PS34, thymine or cytosine at PS35, thymine or cytosine at PS36, thymine or cytosine at PS37, cytosine or thymine at PS38, cytosine or

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guanine at PS39, adenine or guanine at PS40, guanine or adenine at PS41, cytosine or thymine at PS44

and guanine or adenine at PS45. The invention also provides a collection of IL4Rα isogenes, referred to

herein as an IL4Rα genome anthology.

An IL4Rα isogene may be defined by the combination and order of these polymorphisms in the

isogene, which is referred to herein as an IL4Rα haplotype. Thus, the invention also provides data on the

number of different IL4Rα haplotypes found in the above four population groups. This haplotype data is

useful in methods for deriving an IL4Rα haplotype from an individual's genotype for the IL4Rα gene and

for determining an association between an IL4Rα haplotype and a particular trait.

In another embodiment, the invention provides a polynucleotide comprising a polymorphic

variant of a reference sequence for an IL4Rα cDNA or a fragment thereof. The reference sequence

comprises SEQ ID NO:2 (Fig. 2) and the polymorphic cDNA comprises at least one polymorphism

selected from the group consisting of thymine at a position corresponding to nucleotide 237, adenine at a

position corresponding to nucleotide 244, cytosine at a position corresponding to nucleotide 291, thymine

at a position corresponding to nucleotide 501, adenine at a position corresponding to nucleotide 554,

cytosine at a position corresponding to nucleotide 939, thymine at a position corresponding to nucleotide

1242, thymine at a position corresponding to nucleotide 1293, cytosine at a position corresponding to

nucleotide 1299, thymine at a position corresponding to nucleotide 1701, adenine at a position

corresponding to nucleotide 1735, thymine at a position corresponding to nucleotide 2023, guanine at a

position corresponding to nucleotide 2254 and cytosine at a position corresponding to nucleotide 2397 .

In a preferred embodiment, the polymorphic variant comprises one or more additional polymorphisms -

selected from the group consisting of guanine at a position corresponding to 223, cytosine at a position

corresponding to nucleotide 1199, cytosine at a position corresponding to 1291, cytosine at a position

corresponding to nucleotide 1507 and guanine at a position corresponding to 1737.

Polynucleotides complementary to these IL4Rα genomic and cDNA variants are also provided by

the invention.

In other embodiments, the invention provides a recombinant expression vector comprising one of

the polymorphic genomic variants operably linked to expression regulatory elements as well as a

recombinant host cell transformed or transfected with the expression vector. The recombinant vector and

host cell may be used to express IL4Rα for protein structure analysis and drug binding studies.

In yet another embodiment, the invention provides a polypeptide comprising a polymorphic

variant of a reference amino acid sequence for the IL4Rα protein. The reference amino acid sequence

comprises SEQ ID NO:3 (Fig. 3) and the polymorphic variant comprises at least one variant amino acid

selected from the group consisting of threonine at a position corresponding to amino acid 82, histidine at

a position corresponding to amino acid 185, isoleucine at a position corresponding to amino acid 579,

serine at a position corresponding to amino acid 675, and alanine at a position corresponding to amino

acid 752. In some embodiments, the polymorphic variant also comprises at least one variant amino acid

selected from the group consisting of valine at a position corresponding to amino acid 75, alanine at a position corresponding to amino acid 400, arginine at a position correpsonding to amino acid 431, proline at a position corresponding to amino acid 503, and arginine at a position corresponding to amino acid 576. A polymorphic variant of IL4Rα is useful in studying the effect of the variation on the biological

5   activity of IL4Rα as well as studying the binding affinity of candidate drugs targeting IL4Rα for the treatment of allergies, asthma, and other immune responses.

The present invention also provides antibodies that recognize and bind to the above polymorphic IL4Rα protein variant. Such antibodies can be utilized in a variety of diagnostic and prognostic formats and therapeutic methods.

10   In other embodiments, the invention provides methods, compositions, and kits for haplotyping and/or genotyping the IL4Rα gene in an individual. The methods involve identifying the nucleotide or nucleotide pair present at one or more polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and

15   PS45 in one or both copies of the IL4Rα gene from the individual. The compositions contain oligonucleotide probes and primers designed to specifically hybridize to one or more target regions containing, or that are adjacent to, a polymorphic site. The methods and compositions for establishing the genotype or haplotype of an individual at the novel polymorphic sites described herein are useful for studying the effect of the polymorphisms in the etiology of diseases affected by the expression and

20   function of the IL4Rα protein, studying the efficacy of drugs targeting IL4Rα, predicting individual susceptibility to diseases affected by the expression and function of the IL4Rα protein and predicting individual responsiveness to drugs targeting IL4Rα.

In yet another embodiment, the invention provides a method for identifying an association between a genotype or haplotype and a trait. In preferred embodiments, the trait is susceptibility to a

25   disease, severity of a disease, the staging of a disease or response to a drug. Such methods have applicability in developing diagnostic tests and therapeutic treatments for allergies, asthma, and other immune responses.

The present invention also provides transgenic animals comprising one of the IL4Rα genomic polymorphic variants described herein and methods for producing such animals. The transgenic animals

30   are useful for studying expression of the IL4Rα isogenes *in vivo*, for *in vivo* screening and testing of drugs targeted against IL4Rα protein, and for testing the efficacy of therapeutic agents and compounds for allergies, asthma, and other immune responses in a biological system.

The present invention also provides a computer system for storing and displaying polymorphism data determined for the IL4Rα gene. The computer system comprises a computer processing unit; a

35   display; and a database containing the polymorphism data. The polymorphism data includes the polymorphisms, the genotypes and the haplotypes identified for the IL4Rα gene in a reference

population. In a preferred embodiment, the computer system is capable of producing a display showing IL4Rα haplotypes organized according to their evolutionary relationships.

BRIEF DESCRIPTION OF THE DRAWINGS

5   Figure 1 illustrates a reference sequence for the IL4Rα gene that is the reverse complement of part of Genbank Accession Number AC004525.1; contiguous lines; SEQ ID NO:1), with the underlines indicating the start and stop codons, shading indicating the reference coding sequence, and the bold nucleotides indicating the polymorphic sites and polymorphisms identified by Applicants in a reference population.

10   Figure 2 illustrates a reference sequence for the IL4Rα coding sequence (GenBank Accession Number X52425; contiguous lines; SEQ ID NO:2), with the underlines indicating the start and stop codons, and the bold nucleotides indicating the polymorphic sites and polymorphisms identified by Applicants in a reference population.

          Figure 3 illustrates a reference sequence for the IL4Rα protein (GenBank Accession Number
15 CAA36672; contiguous lines; SEQ ID NO:3), with the bold amino acids indicating the amino acid variations caused by the polymorphisms of Fig. 2.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

          The present invention is based on the discovery of novel variants of the IL4Rα gene. As
20 described in more detail below, the inventors herein discovered 38 novel polymorphic sites by characterizing the IL4Rα gene found in genomic DNAs isolated from Index Repository IA that contains immortalized cell lines from one chimpanzee and 93 human individuals and Index Repository IB that contains 70 human individuals. Theses two repositories contain 51 individuals in common.

          The human individuals in Index Repository IA included a reference population of 79 unrelated
25 individuals self-identified as belonging to one of four major population groups: Caucasian (22 individuals), African descent (20 individuals) Asian (20 individuals) Hispanic/Latino (17 individuals). To the extent possible, the members of this reference population were organized into population subgroups by the self-identified ethnogeographic origin of their four grandparents as shown in Table 1 below. In addition, Index Repository IA contains three unrelated indigenous American Indians (one from
30 each of North, Central, and South America), one three-generation Caucasian family (From the CEPH Utah cohort) and one two-generation African-American family.

Table 1. Population Groups in Index Repository IA

Population Group	Population Subgroup	No. of Individuals
African descent		20
	Sierra Leone	1
Asian		20
	Burma	1
	China	3
	Japan	6
	Korea	1
	Philippines	5
	Vietnam	4
Caucasian		22
	British Isles	3
	British Isles/Central	4
	British Isles/Eastern	1
	Central/Eastern	1
	Eastern	3
	Central/Mediterranean	1
	Mediterranean	2
	Scandinavian	2
Hispanic/Latino		17
	Caribbean	7
	Caribbean (Spanish Descent)	2
	Central American (Spanish Descent)	1
	Mexican American	4
	South American (Spanish Descent)	3

Index Repository IB contains a reference population of 70 human individuals comprised of 4

5   three-generation families (from the CEPH Utah cohort) as well as unrelated African-American, Asian,

and Caucasian individuals. A total of 38 individuals in this reference population are unrelated.

Using the IL4Rα genotypes identified in the Index Repositories and the methodology described

in the Examples below, the inventors herein also determined the haplotypes found on each chromosome

for most human members of this repository. The IL4α genotypes and haplotypes found in the Index

10   Repositories include those shown in Tables 4 and 5, respectively. The polymorphism and haplotype data

disclosed herein are useful for studying population diversity, anthropological lineage, the significance of

diversity and lineage at the phenotypic level, paternity testing, forensic applications, and for identifying

associations between the IL4Rα genetic variation and a trait such as level of drug response or

susceptibility to disease.

15   In the context of this disclosure, the following terms shall be defined as follows unless otherwise

indicated:

Allele - A particular form of a genetic locus, distinguished from other forms by its particular

nucleotide sequence.

Candidate Gene – A gene which is hypothesized to be responsible for a disease, condition, or the

response to a treatment, or to be correlated with one of these.

   Gene - A segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

   Genotype – An unphased 5′ to 3′ sequence of nucleotide pair(s) found at one or more polymorphic sites in a locus on a pair of homologous chromosomes in an individual. As used herein, genotype includes a full-genotype and/or a sub-genotype as described below.

   Full-genotype – The unphased 5′ to 3′ sequence of nucleotide pairs found at all known polymorphic sites in a locus on a pair of homologous chromosomes in a single individual.

   Sub-genotype – The unphased 5′ to 3′ sequence of nucleotides seen at a subset of the known polymorphic sites in a locus on a pair of homologous chromosomes in a single individual.

   Genotyping – A process for determining a genotype of an individual.

   Haplotype – A 5′ to 3′ sequence of nucleotides found at one or more polymorphic sites in a locus on a single chromosome from a single individual. As used herein, haplotype includes a full-haplotype and/or a sub-haplotype as described below.

   Full-haplotype – The 5′ to 3′ sequence of nucleotides found at all known polymorphic sites in a locus on a single chromosome from a single individual.

   Sub-haplotype – The 5′ to 3′ sequence of nucleotides seen at a subset of the known polymorphic sites in a locus on a single chromosome from a single individual.

   Haplotype pair – The two haplotypes found for a locus in a single individual.

   Haplotyping – A process for determining one or more haplotypes in an individual and includes use of family pedigrees, molecular techniques and/or statistical inference.

   Haplotype data - Information concerning one or more of the following for a specific gene: a listing of the haplotype pairs in each individual in a population; a listing of the different haplotypes in a population; frequency of each haplotype in that or other populations, and any known associations between one or more haplotypes and a trait.

   Isoform – A particular form of a gene, mRNA, cDNA or the protein encoded thereby, distinguished from other forms by its particular sequence and/or structure.

   Isogene – One of the isoforms of a gene found in a population. An isogene contains all of the polymorphisms present in the particular isoform of the gene.

   Isolated – As applied to a biological molecule such as RNA, DNA, oligonucleotide, or protein, isolated means the molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to a complete absence of such material or to absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with the methods of the present invention.

   Locus - A location on a chromosome or DNA molecule corresponding to a gene or a physical or phenotypic feature.

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Naturally- ccurring – A term used to designate that the object it is applied to, e.g., naturally-occurring polynucleotide or polypeptide, can be isolated from a source in nature and which has not been intentionally modified by man.

Nucleotide pair – The nucleotides found at a polymorphic site on the two copies of a
5   chromosome from an individual.

Phased – As applied to a sequence of nucleotide pairs for two or more polymorphic sites in a locus, phased means the combination of nucleotides present at those polymorphic sites on a single copy of the locus is known.

Polymorphic site (PS) – A position within a locus at which at least two alternative sequences are
10   found in a population, the most frequent of which has a frequency of no more than 99%.

Polymorphic variant – A gene, mRNA, cDNA, polypeptide or peptide whose nucleotide or amino acid sequence varies from a reference sequence due to the presence of a polymorphism in the gene.

Polymorphism – The sequence variation observed in an individual at a polymorphic site. Polymorphisms include nucleotide substitutions, insertions, deletions and microsatellites and may, but
15   need not, result in detectable differences in gene expression or protein function.

Polymorphism data – Information concerning one or more of the following for a specific gene: location of polymorphic sites; sequence variation at those sites; frequency of polymorphisms in one or more populations; the different genotypes and/or haplotypes determined for the gene; frequency of one or more of these genotypes and/or haplotypes in one or more populations; any known association(s) between
20   a trait and a genotype or a haplotype for the gene.

Polymorphism Database – A collection of polymorphism data arranged in a systematic or methodical way and capable of being individually accessed by electronic or other means.

Polynucleotide – A nucleic acid molecule comprised of single-stranded RNA or DNA or comprised of complementary, double-stranded DNA.

25   **Population Group** – A group of individuals sharing a common ethnogeographic origin.

Reference Population – A group of subjects or individuals who are predicted to be representative of the genetic variation found in the general population. Typically, the reference population represents the genetic variation in the population at a certainty level of at least 85%, preferably at least 90%, more preferably at least 95% and even more preferably at least 99%.

30   **Single Nucleotide Polymorphism (SNP)** – Typically, the specific pair of nucleotides observed at a single polymorphic site. In rare cases, three or four nucleotides may be found.

Subject – A human individual whose genotypes or haplotypes or response to treatment or disease state are to be determined.

Treatment - A stimulus administered internally or externally to a subject.

35   **Unphased** – As applied to a sequence of nucleotide pairs for two or more polymorphic sites in a locus, unphased means the combination of nucleotides present at those polymorphic sites on a single copy of the locus is not known.

The inventors herein have discovered 38 novel polymorphic sites , and confirmed the existence of 7 other sites, in th IL4Rα gene. The polymorphic sites identified by the inventors are referred to as PS1-45 to designate the order in which they are located in the gene (see Table 3 below), with the novel polymorphic site referred to as PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14,
5   PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45 and the previously reported polymorphic sites referred to as PS5, PS24, PS26, PS29, PS31, PS42, and PS43.

Thus, in one embodiment, the invention provides an isolated polynucleotide comprising a polymorphic variant of the IL4Rα gene or a fragment of the gene which contains at least one of the novel
10   polymorphic sites described herein. The nucleotide sequence of a variant IL4Rα gene is identical to the reference genomic sequence for those portions of the gene examined, as described in the Examples below, except that it comprises a different nucleotide at one or more of the novel polymorphic sites PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40,
15   PS41, PS44, and PS45,and may also comprise one or more additional polymorphisms selected from the group consisting of PS5, PS24, PS26, PS29, PS31, PS42, and PS43. Similarly, the nucleotide sequence of a variant fragment of the IL4Rα gene is identical to the corresponding portion of the reference sequence except for having a different nucleotide at one or more of the novel polymorphic sites described herein. Thus, the invention specifically does not include polynucleotides comprising a nucleotide
20   sequence identical to the reference sequence (or other reported IL4Rα sequences) or to portions of the reference sequence (or other reported IL4Rα sequences), except for genotyping oligonucleotides as described below.

The location of a polymorphism in a variant gene or fragment is identified by aligning its sequence against SEQ ID NO:1. The polymorphism is selected from the group consisting of guanine at
25   PS1, thymine at PS2, thymine at PS3, cytosine at PS4, thymine at PS6, adenine at PS7, cytosine at PS8, thymine at PS9, thymine at PS10, adenine at PS11, adenine at PS12, thymine at PS13, thymine at PS14, adenine at PS15, thymine at PS16, adenine at PS17, thymine at PS18, adenine at PS19, cytosine at PS20, cytosine at PS21, thymine at PS22, cytosine at PS23, thymine at PS25, thymine at PS27, cytosine at PS28, thymine at PS30, adenine at PS32, thymine at PS33, guanine at PS34, cytosine at PS35, cytosine at
30   PS36, cytosine at PS37, thymine at PS38, guanine at PS39, guanine at PS40, adenine at PS41, thymine at PS44, and adenine at PS45. In a preferred embodiment, the polymorphic variant comprises a naturally-occurring isogene of the IL4Rα gene which is defined by any one of haplotypes 1-53 shown in Table 5 below.

Polymorphic variants of the invention may be prepared by isolating a clone containing the IL4Rα
35   gene from a human genomic library. The clone may be sequenced to determine the identity of the nucleotides at the polymorphic sites described herein. Any particular variant claimed herein could be

prepared from this clone by performing *in vitro* mutagenesis using procedures well-known in the art.

IL4Rα isogenes may be isolated using any method that allows separation of the two "copies" of the IL4Rα gene present in an individual, which, as readily understood by the skilled artisan, may be the same allele or different alleles. Separation methods include targeted *in vivo* cloning (TIVC) in yeast as

5   described in WO 98/01573, U.S. Patent No. 5,866,404, and copending U.S. application Serial No. 08/987,966. Another method, which is described in copending U.S. Application Serial No. 08/987,966, uses an allele specific oligonucleotide in combination with primer extension and exonuclease degradation to generate hemizygous DNA targets. Yet other methods are single molecule dilution (SMD) as described in Ruaño et al., Proc. Natl. Acad. Sci. 87:6296-6300, 1990; and allele specific PCR (Ruaño et

10   al., 17 Nucleic Acids. Res. 8392, 1989; Ruaño et al., 19 Nucleic Acids Res. 6877-6882, 1991; Michalatos-Beloin et al., 24 Nucleic Acids Res. 4841-4843, 1996).

The invention also provides IL4Rα genome anthologies, which are collections of IL4Rα isogenes found in a given population. The population may be any group of at least two individuals, including but not limited to a reference population, a population group, a family population, a clinical population, and a

15   same sex population. An IL4Rα genome anthology may comprise individual IL4Rα isogenes stored in separate containers such as microtest tubes, separate wells of a microtitre plate and the like. Alternatively, two or more groups of the IL4Rα isogenes in the anthology may be stored in separate containers. Individual isogenes or groups of isogenes in a genome anthology may be stored in any convenient and stable form, including but not limited to in buffered solutions, as DNA precipitates,

20   freeze-dried preparations and the like. A preferred IL4Rα genome anthology of the invention comprises a set of isogenes defined by the haplotypes shown in Table 5 below.

An isolated polynucleotide containing a polymorphic variant nucleotide sequence of the invention may be operably linked to one or more expression regulatory elements in a recombinant expression vector capable of being propagated and expressing the encoded IL4Rα protein in a prokaryotic or a eukaryotic

25   host cell. Examples of expression regulatory elements which may be used include, but are not limited to, the lac system, operator and promoter regions of phage lambda, yeast promoters, and promoters derived from vaccinia virus, adenovirus, retroviruses, or SV40. Other regulatory elements include, but are not limited to, appropriate leader sequences, termination codons, polyadenylation signals, and other sequences required for the appropriate transcription and subsequent translation of the nucleic acid

30   sequence in a given host cell. Of course, the correct combinations of expression regulatory elements will depend on the host system used. In addition, it is understood that the expression vector contains any additional elements necessary for its transfer to and subsequent replication in the host cell. Examples of such elements include, but are not limited to, origins of replication and selectable markers. Such expression vectors are commercially available or are readily constructed using methods known to those in

35   the art (e.g., F. Ausubel et al., 1987, in "Current Protocols in Molecular Biology", John Wiley and Sons, New York, New York). Host cells which may be used to express the variant IL4Rα sequences of the

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inv ntion include, but are not limited to, eukaryotic and mammalian cells, such as animal, plant, insect
and yeast cells, and prokaryotic cells, such as E. coli, or algal cells as known in the art. The recombinant
expression vector may be introduced into the host cell using any method known to those in the art
including, but not limited to, microinjection, electroporation, particle bombardment, transduction, and

5   transfection using DEAE-dextran, lipofection, or calcium phosphate (see e.g., Sambrook et al. (1989) in
"Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Press, Plainview, New York). In a
preferred aspect, eukaryotic expression vectors that function in eukaryotic cells, and preferably
mammalian cells, are used. Non-limiting examples of such vectors include vaccinia virus vectors,
adenovirus vectors, herpes virus vectors, and baculovirus transfer vectors. Preferred eukaryotic cell lines

10   include COS cells, CHO cells, HeLa cells, NIH/3T3 cells, and embryonic stem cells (Thomson, J. A. et
al., 1998 Science 282:1145-1147). Particularly preferred host cells are mammalian cells.

       As will be readily recognized by the skilled artisan, expression of polymorphic variants of the
IL4Rα gene will produce IL4Rα mRNAs varying from each other at any polymorphic site retained in the
spliced and processed mRNA molecules. These mRNAs can be used for the preparation of an IL4Rα

15   cDNA comprising a nucleotide sequence which is a polymorphic variant of the IL4Rα reference coding
sequence shown in Figure 2. Thus, the invention also provides IL4Rα mRNAs and corresponding
cDNAs which comprise a nucleotide sequence that is identical to SEQ ID NO:2 (Fig. 2), or its
corresponding RNA sequence, except for having one or more polymorphisms selected from the group
consisting of thymine at a position corresponding to nucleotide 237, adenine at a position corresponding

20   to nucleotide 244, cytosine at a position corresponding to nucleotide 291, thymine at a position
corresponding to nucleotide 501, adenine at a position corresponding to nucleotide 554, cytosine at a
position corresponding to nucleotide 939, thymine at a position corresponding to nucleotide 1242,
thymine at a position corresponding to nucleotide 1293, cytosine at a position corresponding to nucleotide
1299, thymine at a position corresponding to nucleotide 1701, adenine at a position corresponding to

25   nucleotide 1735, thymine at a position corresponding to nucleotide 2023, guanine at a position
corresponding to nucleotide 2254 and cytosine at a position corresponding to nucleotide 2397, and may
also comprise one or more additional polymorphisms selected from the group consisting of guanine at a
position corresponding to 223, cytosine at a position corresponding to nucleotide 1199, cytosine at a
position corresponding to 1291, cytosine at a position corresponding to nucleotide 1507 and guanine at a

30   position corresponding to 1737. Fragments of these variant mRNAs and cDNAs are included in the scope
of the invention, provided they contain the novel polymorphisms described herein. The invention
specifically excludes polynucleotides identical to previously identified and characterized IL4Rα cDNAs
and fragments thereof. Polynucleotides comprising a variant RNA or DNA sequence may be isolated
from a biological sample using well-known molecular biological procedures or may be chemically

35   synthesized.

       Genomic and cDNA fragments of the invention comprise at least one novel polymorphic site
identified herein and have a length of at least 10 nucleotides and may range up to the full length of the

gene. Preferably, a fragment according to the present invention is between 100 and 3000 nucleotides in length, and more preferably between 200 and 2000 nucleotides in length, and most preferably between 500 and 1000 nucleotides in length.

     In describing the polymorphic sites identified herein, reference is made to the sense strand of the gene for convenience. However, as recognized by the skilled artisan, nucleic acid molecules containing the IL4Rα gene may be complementary double stranded molecules and thus reference to a particular site on the sense strand refers as well to the corresponding site on the complementary antisense strand. Thus, reference may be made to the same polymorphic site on either strand and an oligonucleotide may be designed to hybridize specifically to either strand at a target region containing the polymorphic site. Thus, the invention also includes single-stranded polynucleotides which are complementary to the sense strand of the IL4Rα genomic variants described herein.

     Polynucleotides comprising a polymorphic gene variant or fragment may be useful for therapeutic purposes. For example, where a patient could benefit from expression, or increased expression, of a particular IL4Rα protein isoform, an expression vector encoding the isoform may be administered to the patient. The patient may be one who lacks the IL4Rα isogene encoding that isoform or may already have at least one copy of that isogene.

     In other situations, it may be desirable to decrease or block expression of a particular IL4Rα isogene. Expression of an IL4Rα isogene may be turned off by transforming a targeted organ, tissue or cell population with an expression vector that expresses high levels of untranslatable mRNA for the isogene. Alternatively, oligonucleotides directed against the regulatory regions (e.g., promoter, introns, enhancers, 3′ untranslated region) of the isogene may block transcription. Oligonucleotides targeting the transcription initiation site, e.g., between positions −10 and +10 from the start site are preferred. Similarly, inhibition of transcription can be achieved using oligonucleotides that base-pair with region(s) of the isogene DNA to form triplex DNA (see e.g., Gee et al. in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing Co., Mt. Kisco, N.Y., 1994). Antisense oligonucleotides may also be designed to block translation of IL4Rα mRNA transcribed from a particular isogene. It is also contemplated that ribozymes may be designed that can catalyze the specific cleavage of IL4Rα mRNA transcribed from a particular isogene.

     The oligonucleotides may be delivered to a target cell or tissue by expression from a vector introduced into the cell or tissue *in vivo* or *ex vivo*. Alternatively, the oligonucleotides may be formulated as a pharmaceutical composition for administration to the patient. Oligoribonucleotides and/or oligodeoxynucleotides intended for use as antisense oligonucleotides may be modified to increase stability and half-life. Possible modifications include, but are not limited to phosphorothioate or 2′ O-methyl linkages, and the inclusion of nontraditional bases such as inosine and queosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytosine, guanine, thymine, and uracil which are not as easily recognized by endogenous nucleases.

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The invention also provides an isolated polypeptide comprising a polymorphic variant of the reference IL4Rα amino acid sequence shown in 3. The location of a variant amino acid in an IL4Rα polypeptide or fragment of the invention is identified by aligning its sequence against Fig. 3. An IL4Rα protein variant of the invention comprises an amino acid sequence identical to SEQ ID NO: 3 except for

5   having one or more variant amino acids selected from the group consisting of threonine at a position corresponding to amino acid 82, histidine at a position corresponding to amino acid 185, isoleucine at a position corresponding to amino acid 579, serine at a position corresponding to amino acid 675, and alanine at a position corresponding to amino acid 752, and may also comprise one or more additional variant amino acids selected from the group consisting of valine at a position corresponding to amino acid

10   75, alanine at a position corresponding to amino acid 400, arginine at a position correpsonding to amino acid 431, proline at a position corresponding to amino acid 503, and arginine at a position corresponding to amino acid 576. The invention specifically excludes amino acid sequences identical to those previously identified for IL4Rα, including SEQ ID NO: 3, and previously described fragments thereof. IL4Rα protein variants included within the invention comprise all amino acid sequences based on SEQ ID NO: 3

15   and having the combination of amino acid variations described in Table 2 below. In preferred embodiments, an IL4Rα protein variant of the invention is encoded by an isogene defined by one of the observed haplotypes shown in Table 5.

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Table2. Novel Polymorphic Variant of IL4Rα

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
1	I	A	R	E	C	S	Q	V	P	A
2	I	A	R	E	C	S	Q	V	S	S
3	I	A	R	E	C	S	Q	V	S	A
4	I	A	R	E	C	S	Q	I	P	S
5	I	A	R	E	C	S	Q	I	P	A
6	I	A	R	E	C	S	Q	I	S	S
7	I	A	R	E	C	S	Q	I	S	A
8	I	A	R	E	C	S	R	V	P	A
9	I	A	R	E	C	S	R	V	S	S
10	I	A	R	E	C	S	R	V	S	A
11	I	A	R	E	C	S	R	I	P	S
12	I	A	R	E	C	S	R	I	P	A
13	I	A	R	E	C	S	R	I	S	S
14	I	A	R	E	C	S	R	I	S	A
15	I	A	R	E	C	P	Q	V	P	A
16	I	A	R	E	C	P	Q	V	S	S
17	I	A	R	E	C	P	Q	V	S	A
18	I	A	R	E	C	P	Q	I	P	S
19	I	A	R	E	C	P	Q	I	P	A
20	I	A	R	E	C	P	Q	I	S	S
21	I	A	R	E	C	P	Q	I	S	A
22	I	A	R	E	C	P	R	V	P	A
23	I	A	R	E	C	P	R	V	S	S
24	I	A	R	E	C	P	R	V	S	A
25	I	A	R	E	C	P	R	I	P	S
26	I	A	R	E	C	P	R	I	P	A
27	I	A	R	E	C	P	R	I	S	S
28	I	A	R	E	C	P	R	I	S	A
29	I	A	R	E	R	S	Q	V	P	A
30	I	A	R	E	R	S	Q	V	S	S
31	I	A	R	E	R	S	Q	V	S	A
32	I	A	R	E	R	S	Q	I	P	S
33	I	A	R	E	R	S	Q	I	P	A
34	I	A	R	E	R	S	Q	I	S	S
35	I	A	R	E	R	S	Q	I	S	A
36	I	A	R	E	R	S	R	V	P	A
37	I	A	R	E	R	S	R	V	S	S
38	I	A	R	E	R	S	R	V	S	A
39	I	A	R	E	R	S	R	I	P	S
40	I	A	R	E	R	S	R	I	P	A
41	I	A	R	E	R	S	R	I	S	S
42	I	A	R	E	R	S	R	I	S	A
43	I	A	R	E	R	P	Q	V	P	A
44	I	A	R	E	R	P	Q	V	S	S
45	I	A	R	E	R	P	Q	V	S	A
46	I	A	R	E	R	P	Q	I	P	S
47	I	A	R	E	R	P	Q	I	P	A
48	I	A	R	E	R	P	Q	I	S	S
49	I	A	R	E	R	P	Q	I	S	A
50	I	A	R	E	R	P	R	V	P	A
51	I	A	R	E	R	P	R	V	S	S
52	I	A	R	E	R	P	R	V	S	A
53	I	A	R	E	R	P	R	I	P	S

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)									
Polymorphic Variant Number	Amino Acid Position and Identities								
	75	82	185	400	431	503	576	579	675	752
54	I	A	R	E	R	P	R	I	P	A
55	I	A	R	E	R	P	R	I	S	S
56	I	A	R	E	R	P	R	I	S	A
57	I	A	R	A	C	S	Q	V	P	A
58	I	A	R	A	C	S	Q	V	S	S
59	I	A	R	A	C	S	Q	V	S	A
60	I	A	R	A	C	S	Q	I	P	S
61	I	A	R	A	C	S	Q	I	P	A
62	I	A	R	A	C	S	Q	I	S	S
63	I	A	R	A	C	S	Q	I	S	A
64	I	A	R	A	C	S	R	V	P	A
65	I	A	R	A	C	S	R	V	S	S
66	I	A	R	A	C	S	R	V	S	A
67	I	A	R	A	C	S	R	I	P	S
68	I	A	R	A	C	S	R	I	P	A
69	I	A	R	A	C	S	R	I	S	S
70	I	A	R	A	C	S	R	I	S	A
71	I	A	R	A	C	P	Q	V	P	A
72	I	A	R	A	C	P	Q	V	S	S
73	I	A	R	A	C	P	Q	V	S	A
74	I	A	R	A	C	P	Q	I	P	S
75	I	A	R	A	C	P	Q	I	P	A
76	I	A	R	A	C	P	Q	I	S	S
77	I	A	R	A	C	P	Q	I	S	A
78	I	A	R	A	C	P	R	V	P	A
79	I	A	R	A	C	P	R	V	S	S
80	I	A	R	A	C	P	R	V	S	A
81	I	A	R	A	C	P	R	I	P	S
82	I	A	R	A	C	P	R	I	P	A
83	I	A	R	A	C	P	R	I	S	S
84	I	A	R	A	C	P	R	I	S	A
85	I	A	R	A	R	S	Q	V	P	A
86	I	A	R	A	R	S	Q	V	S	S
87	I	A	R	A	R	S	Q	V	S	A
88	I	A	R	A	R	S	Q	I	P	S
89	I	A	R	A	R	S	Q	I	P	A
90	I	A	R	A	R	S	Q	I	S	S
91	I	A	R	A	R	S	Q	I	S	A
92	I	A	R	A	R	S	R	V	P	A
93	I	A	R	A	R	S	R	V	S	S
94	I	A	R	A	R	S	R	V	S	A
95	I	A	R	A	R	S	R	I	P	S
96	I	A	R	A	R	S	R	I	P	A
97	I	A	R	A	R	S	R	I	S	S
98	I	A	R	A	R	S	R	I	S	A
99	I	A	R	A	R	P	Q	V	P	A
100	I	A	R	A	R	P	Q	V	S	S
101	I	A	R	A	R	P	Q	V	S	A
102	I	A	R	A	R	P	Q	I	P	S
103	I	A	R	A	R	P	Q	I	P	A
104	I	A	R	A	R	P	Q	I	S	S
105	I	A	R	A	R	P	Q	I	S	A
106	I	A	R	A	R	P	R	V	P	A

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
107	I	A	R	A	R	P	R	V	S	S
108	I	A	R	A	R	P	R	V	S	A
109	I	A	R	A	R	P	R	I	P	S
110	I	A	R	A	R	P	R	I	P	A
111	I	A	R	A	R	P	R	I	S	S
112	I	A	R	A	R	P	R	I	S	A
113	I	A	H	E	C	S	Q	V	P	S
114	I	A	H	E	C	S	Q	V	P	A
115	I	A	H	E	C	S	Q	V	S	S
116	I	A	H	E	C	S	Q	V	S	A
117	I	A	H	E	C	S	Q	I	P	S
118	I	A	H	E	C	S	Q	I	P	A
119	I	A	H	E	C	S	Q	I	S	S
120	I	A	H	E	C	S	Q	I	S	A
121	I	A	H	E	C	S	R	V	P	S
122	I	A	H	E	C	S	R	V	P	A
123	I	A	H	E	C	S	R	V	S	S
124	I	A	H	E	C	S	R	V	S	A
125	I	A	H	E	C	S	R	I	P	S
126	I	A	H	E	C	S	R	I	P	A
127	I	A	H	E	C	S	R	I	S	S
128	I	A	H	E	C	S	R	I	S	A
129	I	A	H	E	C	P	Q	V	P	S
130	I	A	H	E	C	P	Q	V	P	A
131	I	A	H	E	C	P	Q	V	S	S
132	I	A	H	E	C	P	Q	V	S	A
133	I	A	H	E	C	P	Q	I	P	S
134	I	A	H	E	C	P	Q	I	P	A
135	I	A	H	E	C	P	Q	I	S	S
136	I	A	H	E	C	P	Q	I	S	A
137	I	A	H	E	C	P	R	V	P	S
138	I	A	H	E	C	P	R	V	P	A
139	I	A	H	E	C	P	R	V	S	S
140	I	A	H	E	C	P	R	V	S	A
141	I	A	H	E	C	P	R	I	P	S
142	I	A	H	E	C	P	R	I	P	A
143	I	A	H	E	C	P	R	I	S	S
144	I	A	H	E	C	P	R	I	S	A
145	I	A	H	E	R	S	Q	V	P	S
146	I	A	H	E	R	S	Q	V	P	A
147	I	A	H	E	R	S	Q	V	S	S
148	I	A	H	E	R	S	Q	V	S	A
149	I	A	H	E	R	S	Q	I	P	S
150	I	A	H	E	R	S	Q	I	P	A
151	I	A	H	E	R	S	Q	I	S	S
152	I	A	H	E	R	S	Q	I	S	A
153	I	A	H	E	R	S	R	V	P	S
154	I	A	H	E	R	S	R	V	P	A
155	I	A	H	E	R	S	R	V	S	S
156	I	A	H	E	R	S	R	V	S	A
157	I	A	H	E	R	S	R	I	P	S
158	I	A	H	E	R	S	R	I	P	A
159	I	A	H	E	R	S	R	I	S	S

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
160	I	A	H	E	R	S	R	I	S	A
161	I	A	H	E	R	P	Q	V	P	S
162	I	A	H	E	R	P	Q	V	P	A
163	I	A	H	E	R	P	Q	V	S	S
164	I	A	H	E	R	P	Q	V	S	A
165	I	A	H	E	R	P	Q	I	P	S
166	I	A	H	E	R	P	Q	I	P	A
167	I	A	H	E	R	P	Q	I	S	S
168	I	A	H	E	R	P	Q	I	S	A
169	I	A	H	E	R	P	R	V	P	S
170	I	A	H	E	R	P	R	V	P	A
171	I	A	H	E	R	P	R	V	S	S
172	I	A	H	E	R	P	R	V	S	A
173	I	A	H	E	R	P	R	I	P	S
174	I	A	H	E	R	P	R	I	P	A
175	I	A	H	E	R	P	R	I	S	S
176	I	A	H	E	R	P	R	I	S	A
177	I	A	H	A	C	S	Q	V	P	S
178	I	A	H	A	C	S	Q	V	P	A
179	I	A	H	A	C	S	Q	V	S	S
180	I	A	H	A	C	S	Q	V	S	A
181	I	A	H	A	C	S	Q	I	P	S
182	I	A	H	A	C	S	Q	I	P	A
183	I	A	H	A	C	S	Q	I	S	S
184	I	A	H	A	C	S	Q	I	S	A
185	I	A	H	A	C	S	R	V	P	S
186	I	A	H	A	C	S	R	V	P	A
187	I	A	H	A	C	S	R	V	S	S
188	I	A	H	A	C	S	R	V	S	A
189	I	A	H	A	C	S	R	I	P	S
190	I	A	H	A	C	S	R	I	P	A
191	I	A	H	A	C	S	R	I	S	S
192	I	A	H	A	C	S	R	I	S	A
193	I	A	H	A	C	P	Q	V	P	S
194	I	A	H	A	C	P	Q	V	P	A
195	I	A	H	A	C	P	Q	V	S	S
196	I	A	H	A	C	P	Q	V	S	A
197	I	A	H	A	C	P	Q	I	P	S
198	I	A	H	A	C	P	Q	I	P	A
199	I	A	H	A	C	P	Q	I	S	S
200	I	A	H	A	C	P	Q	I	S	A
201	I	A	H	A	C	P	R	V	P	S
202	I	A	H	A	C	P	R	V	P	A
203	I	A	H	A	C	P	R	V	S	S
204	I	A	H	A	C	P	R	V	S	A
205	I	A	H	A	C	P	R	I	P	S
206	I	A	H	A	C	P	R	I	P	A
207	I	A	H	A	C	P	R	I	S	S
208	I	A	H	A	C	P	R	I	S	A
209	I	A	H	A	R	S	Q	V	P	S
210	I	A	H	A	R	S	Q	V	P	A
211	I	A	H	A	R	S	Q	V	S	S
212	I	A	H	A	R	S	Q	V	S	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
213	I	A	H	A	R	S	Q	I	P	S
214	I	A	H	A	R	S	Q	I	P	A
215	I	A	H	A	R	S	Q	I	S	S
216	I	A	H	A	R	S	Q	I	S	A
217	I	A	H	A	R	S	R	V	P	S
218	I	A	H	A	R	S	R	V	P	A
219	I	A	H	A	R	S	R	V	S	S
220	I	A	H	A	R	S	R	V	S	A
221	I	A	H	A	R	S	R	I	P	S
222	I	A	H	A	R	S	R	I	P	A
223	I	A	H	A	R	S	R	I	S	S
224	I	A	H	A	R	S	R	I	S	A
225	I	A	H	A	R	P	Q	V	P	S
226	I	A	H	A	R	P	Q	V	P	A
227	I	A	H	A	R	P	Q	V	S	S
228	I	A	H	A	R	P	Q	V	S	A
229	I	A	H	A	R	P	Q	I	P	S
230	I	A	H	A	R	P	Q	I	P	A
231	I	A	H	A	R	P	Q	I	S	S
232	I	A	H	A	R	P	Q	I	S	A
233	I	A	H	A	R	P	R	V	P	S
234	I	A	H	A	R	P	R	V	P	A
235	I	A	H	A	R	P	R	V	S	S
236	I	A	H	A	R	P	R	V	S	A
237	I	A	H	A	R	P	R	I	P	S
238	I	A	H	A	R	P	R	I	P	A
239	I	A	H	A	R	P	R	I	S	S
240	I	A	H	A	R	P	R	I	S	A
241	I	T	R	E	C	S	Q	V	P	S
242	I	T	R	E	C	S	Q	V	P	A
243	I	T	R	E	C	S	Q	V	S	S
244	I	T	R	E	C	S	Q	V	S	A
245	I	T	R	E	C	S	Q	I	P	S
246	I	T	R	E	C	S	Q	I	P	A
247	I	T	R	E	C	S	Q	I	S	S
248	I	T	R	E	C	S	Q	I	S	A
249	I	T	R	E	C	S	R	V	P	S
250	I	T	R	E	C	S	R	V	P	A
251	I	T	R	E	C	S	R	V	S	S
252	I	T	R	E	C	S	R	V	S	A
253	I	T	R	E	C	S	R	I	P	S
254	I	T	R	E	C	S	R	I	P	A
255	I	T	R	E	C	S	R	I	S	S
256	I	T	R	E	C	S	R	I	S	A
257	I	T	R	E	C	P	Q	V	P	S
258	I	T	R	E	C	P	Q	V	P	A
259	I	T	R	E	C	P	Q	V	S	S
260	I	T	R	E	C	P	Q	V	S	A
261	I	T	R	E	C	P	Q	I	P	S
262	I	T	R	E	C	P	Q	I	P	A
263	I	T	R	E	C	P	Q	I	S	S
264	I	T	R	E	C	P	Q	I	S	A
265	I	T	R	E	C	P	R	V	P	S

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
266	I	T	R	E	C	P	R	V	P	A
267	I	T	R	E	C	P	R	V	S	S
268	I	T	R	E	C	P	R	V	S	A
269	I	T	R	E	C	P	R	I	P	S
270	I	T	R	E	C	P	R	I	P	A
271	I	T	R	E	C	P	R	I	S	S
272	I	T	R	E	C	P	R	I	S	A
273	I	T	R	E	R	S	Q	V	P	S
274	I	T	R	E	R	S	Q	V	P	A
275	I	T	R	E	R	S	Q	V	S	S
276	I	T	R	E	R	S	Q	V	S	A
277	I	T	R	E	R	S	Q	I	P	S
278	I	T	R	E	R	S	Q	I	P	A
279	I	T	R	E	R	S	Q	I	S	S
280	I	T	R	E	R	S	Q	I	S	A
281	I	T	R	E	R	S	R	V	P	S
282	I	T	R	E	R	S	R	V	P	A
283	I	T	R	E	R	S	R	V	S	S
284	I	T	R	E	R	S	R	V	S	A
285	I	T	R	E	R	S	R	I	P	S
286	I	T	R	E	R	S	R	I	P	A
287	I	T	R	E	R	S	R	I	S	S
288	I	T	R	E	R	S	R	I	S	A
289	I	T	R	E	R	P	Q	V	P	S
290	I	T	R	E	R	P	Q	V	P	A
291	I	T	R	E	R	P	Q	V	S	S
292	I	T	R	E	R	P	Q	V	S	A
293	I	T	R	E	R	P	Q	I	P	S
294	I	T	R	E	R	P	Q	I	P	A
295	I	T	R	E	R	P	Q	I	S	S
296	I	T	R	E	R	P	Q	I	S	A
297	I	T	R	E	R	P	R	V	P	S
298	I	T	R	E	R	P	R	V	P	A
299	I	T	R	E	R	P	R	V	S	S
300	I	T	R	E	R	P	R	V	S	A
301	I	T	R	E	R	P	R	I	P	S
302	I	T	R	E	R	P	R	I	P	A
303	I	T	R	E	R	P	R	I	S	S
304	I	T	R	E	R	P	R	I	S	A
305	I	T	R	A	C	S	Q	V	P	S
315	I	T	R	A	C	S	R	V	S	S
316	I	T	R	A	C	S	R	V	S	A
317	I	T	R	A	C	S	R	I	P	S
318	I	T	R	A	C	S	R	I	P	A
319	I	T	R	A	C	S	R	I	S	S
320	I	T	R	A	C	S	R	I	S	A
321	I	T	R	A	C	P	Q	V	P	S
322	I	T	R	A	C	P	Q	V	P	A
323	I	T	R	A	C	P	Q	V	S	S
324	I	T	R	A	C	P	Q	V	S	A
325	I	T	R	A	C	P	Q	I	P	S
326	I	T	R	A	C	P	Q	I	P	A
327	I	T	R	A	C	P	Q	I	S	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
328	I	T	R	A	C	P	Q	I	S	A
306	I	T	R	A	C	S	Q	V	P	A
307	I	T	R	A	C	S	Q	V	S	S
308	I	T	R	A	C	S	Q	V	S	A
309	I	T	R	A	C	S	Q	I	P	S
310	I	T	R	A	C	S	Q	I	P	A
311	I	T	R	A	C	S	Q	I	S	S
312	I	T	R	A	C	S	Q	I	S	A
313	I	T	R	A	C	S	R	V	P	S
314	I	T	R	A	C	S	R	V	P	A
329	I	T	R	A	C	P	R	V	P	S
330	I	T	R	A	C	P	R	V	P	A
331	I	T	R	A	C	P	R	V	S	S
332	I	T	R	A	C	P	R	V	S	A
333	I	T	R	A	C	P	R	I	P	S
334	I	T	R	A	C	P	R	I	P	A
335	I	T	R	A	C	P	R	I	S	S
336	I	T	R	A	C	P	R	I	S	A
337	I	T	R	A	R	S	Q	V	P	S
338	I	T	R	A	R	S	Q	V	P	A
339	I	T	R	A	R	S	Q	V	S	S
340	I	T	R	A	R	S	Q	V	S	A
341	I	T	R	A	R	S	Q	I	P	S
342	I	T	R	A	R	S	Q	I	P	A
343	I	T	R	A	R	S	Q	I	S	S
344	I	T	R	A	R	S	Q	I	S	A
345	I	T	R	A	R	S	R	V	P	S
346	I	T	R	A	R	S	R	V	P	A
347	I	T	R	A	R	S	R	V	S	S
348	I	T	R	A	R	S	R	V	S	A
349	I	T	R	A	R	S	R	I	P	S
350	I	T	R	A	R	S	R	I	P	A
351	I	T	R	A	R	S	R	I	S	S
352	I	T	R	A	R	S	R	I	S	A
353	I	T	R	A	R	P	Q	V	P	S
354	I	T	R	A	R	P	Q	V	P	A
355	I	T	R	A	R	P	Q	V	S	S
356	I	T	R	A	R	P	Q	V	S	A
357	I	T	R	A	R	P	Q	I	P	S
358	I	T	R	A	R	P	Q	I	P	A
359	I	T	R	A	R	P	Q	I	S	S
360	I	T	R	A	R	P	Q	I	S	A
361	I	T	R	A	R	P	R	V	P	S
362	I	T	R	A	R	P	R	V	P	A
363	I	T	R	A	R	P	R	V	S	S
364	I	T	R	A	R	P	R	V	S	A
365	I	T	R	A	R	P	R	I	P	S
366	I	T	R	A	R	P	R	I	P	A
367	I	T	R	A	R	P	R	I	S	S
368	I	T	R	A	R	P	R	I	S	A
369	I	T	H	E	C	S	Q	V	P	S
370	I	T	H	E	C	S	Q	V	P	A
371	I	T	H	E	C	S	Q	V	S	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)									
Polymorphic Variant Number	Amino Acid Position and Identities								
	75	82	185	400	431	503	576	579	675	752
372	I	T	H	E	C	S	Q	V	S	A
373	I	T	H	E	C	S	Q	I	P	S
374	I	T	H	E	C	S	Q	I	P	A
375	I	T	H	E	C	S	Q	I	S	S
376	I	T	H	E	C	S	Q	I	S	A
377	I	T	H	E	C	S	R	V	P	S
378	I	T	H	E	C	S	R	V	P	A
379	I	T	H	E	C	S	R	V	S	S
380	I	T	H	E	C	S	R	V	S	A
381	I	T	H	E	C	S	R	I	P	S
382	I	T	H	E	C	S	R	I	P	A
383	I	T	H	E	C	S	R	I	S	S
384	I	T	H	E	C	S	R	I	S	A
385	I	T	H	E	C	P	Q	V	P	S
386	I	T	H	E	C	P	Q	V	P	A
387	I	T	H	E	C	P	Q	V	S	S
388	I	T	H	E	C	P	Q	V	S	A
389	I	T	H	E	C	P	Q	I	P	S
390	I	T	H	E	C	P	Q	I	P	A
391	I	T	H	E	C	P	Q	I	S	S
392	I	T	H	E	C	P	Q	I	S	A
393	I	T	H	E	C	P	R	V	P	S
394	I	T	H	E	C	P	R	V	P	A
395	I	T	H	E	C	P	R	V	S	S
396	I	T	H	E	C	P	R	V	S	A
397	I	T	H	E	C	P	R	I	P	S
398	I	T	H	E	C	P	R	I	P	A
399	I	T	H	E	C	P	R	I	S	S
400	I	T	H	E	C	P	R	I	S	A
401	I	T	H	E	R	S	Q	V	P	S
402	I	T	H	E	R	S	Q	V	P	A
403	I	T	H	E	R	S	Q	V	S	S
404	I	T	H	E	R	S	Q	V	S	A
405	I	T	H	E	R	S	Q	I	P	S
406	I	T	H	E	R	S	Q	I	P	A
407	I	T	H	E	R	S	Q	I	S	S
408	I	T	H	E	R	S	Q	I	S	A
409	I	T	H	E	R	S	R	V	P	S
410	I	T	H	E	R	S	R	V	P	A
411	I	T	H	E	R	S	R	V	S	S
412	I	T	H	E	R	S	R	V	S	A
413	I	T	H	E	R	S	R	I	P	S
414	I	T	H	E	R	S	R	I	P	A
415	I	T	H	E	R	S	R	I	S	S
416	I	T	H	E	R	S	R	I	S	A
417	I	T	H	E	R	P	Q	V	P	S
418	I	T	H	E	R	P	Q	V	P	A
419	I	T	H	E	R	P	Q	V	S	S
420	I	T	H	E	R	P	Q	V	S	A
421	I	T	H	E	R	P	Q	I	P	S
422	I	T	H	E	R	P	Q	I	P	A
423	I	T	H	E	R	P	Q	I	S	S
424	I	T	H	E	R	P	Q	I	S	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
425	I	T	H	E	R	P	R	V	P	S
426	I	T	H	E	R	P	R	V	P	A
427	I	T	H	E	R	P	R	V	S	S
428	I	T	H	E	R	P	R	V	S	A
429	I	T	H	E	R	P	R	I	P	S
430	I	T	H	E	R	P	R	I	P	A
431	I	T	H	E	R	P	R	I	S	S
432	I	T	H	E	R	P	R	I	S	A
433	I	T	H	A	C	S	Q	V	P	S
434	I	T	H	A	C	S	Q	V	P	A
435	I	T	H	A	C	S	Q	V	S	S
436	I	T	H	A	C	S	Q	V	S	A
437	I	T	H	A	C	S	Q	I	P	S
438	I	T	H	A	C	S	Q	I	P	A
439	I	T	H	A	C	S	Q	I	S	S
440	I	T	H	A	C	S	Q	I	S	A
441	I	T	H	A	C	S	R	V	P	S
442	I	T	H	A	C	S	R	V	P	A
443	I	T	H	A	C	S	R	V	S	S
444	I	T	H	A	C	S	R	V	S	A
445	I	T	H	A	C	S	R	I	P	S
446	I	T	H	A	C	S	R	I	P	A
447	I	T	H	A	C	S	R	I	S	S
448	I	T	H	A	C	S	R	I	S	A
449	I	T	H	A	C	P	Q	V	P	S
450	I	T	H	A	C	P	Q	V	P	A
451	I	T	H	A	C	P	Q	V	S	S
452	I	T	H	A	C	P	Q	V	S	A
453	I	T	H	A	C	P	Q	I	P	S
454	I	T	H	A	C	P	Q	I	P	A
455	I	T	H	A	C	P	Q	I	S	S
456	I	T	H	A	C	P	Q	I	S	A
457	I	T	H	A	C	P	R	V	P	S
458	I	T	H	A	C	P	R	V	P	A
459	I	T	H	A	C	P	R	V	S	S
460	I	T	H	A	C	P	R	V	S	A
461	I	T	H	A	C	P	R	I	P	S
462	I	T	H	A	C	P	R	I	P	A
463	I	T	H	A	C	P	R	I	S	S
464	I	T	H	A	C	P	R	I	S	A
465	I	T	H	A	R	S	Q	V	P	S
466	I	T	H	A	R	S	Q	V	P	A
467	I	T	H	A	R	S	Q	V	S	S
468	I	T	H	A	R	S	Q	V	S	A
469	I	T	H	A	R	S	Q	I	P	S
470	I	T	H	A	R	S	Q	I	P	A
471	I	T	H	A	R	S	Q	I	S	S
472	I	T	H	A	R	S	Q	I	S	A
473	I	T	H	A	R	S	R	V	P	S
474	I	T	H	A	R	S	R	V	P	A
475	I	T	H	A	R	S	R	V	S	S
476	I	T	H	A	R	S	R	V	S	A
477	I	T	H	A	R	S	R	I	P	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
478	I	T	H	A	R	S	R	I	P	A
479	I	T	H	A	R	S	R	I	S	S
480	I	T	H	A	R	S	R	I	S	A
481	I	T	H	A	R	P	Q	V	P	S
482	I	T	H	A	R	P	Q	V	P	A
483	I	T	H	A	R	P	Q	V	S	S
484	I	T	H	A	R	P	Q	V	S	A
485	I	T	H	A	R	P	Q	I	P	S
486	I	T	H	A	R	P	Q	I	P	A
487	I	T	H	A	R	P	Q	I	S	S
488	I	T	H	A	R	P	Q	I	S	A
489	I	T	H	A	R	P	R	V	P	S
490	I	T	H	A	R	P	R	V	P	A
491	I	T	H	A	R	P	R	V	S	S
492	I	T	H	A	R	P	R	V	S	A
493	I	T	H	A	R	P	R	I	P	S
494	I	T	H	A	R	P	R	I	P	A
495	I	T	H	A	R	P	R	I	S	S
496	I	T	H	A	R	P	R	I	S	A
497	V	A	R	E	C	S	Q	V	P	A
498	V	A	R	E	C	S	Q	V	S	S
499	V	A	R	E	C	S	Q	V	S	A
500	V	A	R	E	C	S	Q	I	P	S
501	V	A	R	E	C	S	Q	I	P	A
502	V	A	R	E	C	S	Q	I	S	S
503	V	A	R	E	C	S	Q	I	S	A
504	V	A	R	E	C	S	R	V	P	A
505	V	A	R	E	C	S	R	V	S	S
506	V	A	R	E	C	S	R	V	S	A
507	V	A	R	E	C	S	R	I	P	S
508	V	A	R	E	C	S	R	I	P	A
509	V	A	R	E	C	S	R	I	S	S
510	V	A	R	E	C	S	R	I	S	A
511	V	A	R	E	C	P	Q	V	P	A
512	V	A	R	E	C	P	Q	V	S	S
513	V	A	R	E	C	P	Q	V	S	A
514	V	A	R	E	C	P	Q	I	P	S
515	V	A	R	E	C	P	Q	I	P	A
516	V	A	R	E	C	P	Q	I	S	S
517	V	A	R	E	C	P	Q	I	S	A
518	V	A	R	E	C	P	R	V	P	A
519	V	A	R	E	C	P	R	V	S	S
520	V	A	R	E	C	P	R	V	S	A
521	V	A	R	E	C	P	R	I	P	S
522	V	A	R	E	C	P	R	I	P	A
523	V	A	R	E	C	P	R	I	S	S
524	V	A	R	E	C	P	R	I	S	A
525	V	A	R	E	R	S	Q	V	P	A
526	V	A	R	E	R	S	Q	V	S	S
527	V	A	R	E	R	S	Q	V	S	A
528	V	A	R	E	R	S	Q	I	P	S
529	V	A	R	E	R	S	Q	I	P	A
530	V	A	R	E	R	S	Q	I	S	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
531	V	A	R	E	R	S	Q	I	S	A
532	V	A	R	E	R	S	R	V	P	A
533	V	A	R	E	R	S	R	V	S	S
534	V	A	R	E	R	S	R	V	S	A
535	V	A	R	E	R	S	R	I	P	S
536	V	A	R	E	R	S	R	I	P	A
537	V	A	R	E	R	S	R	I	S	S
538	V	A	R	E	R	S	R	I	S	A
539	V	A	R	E	R	P	Q	V	P	A
540	V	A	R	E	R	P	Q	V	S	S
541	V	A	R	E	R	P	Q	V	S	A
542	V	A	R	E	R	P	Q	I	P	S
543	V	A	R	E	R	P	Q	I	P	A
544	V	A	R	E	R	P	Q	I	S	S
545	V	A	R	E	R	P	Q	I	S	A
546	V	A	R	E	R	P	R	V	P	A
547	V	A	R	E	R	P	R	V	S	S
548	V	A	R	E	R	P	R	V	S	A
549	V	A	R	E	R	P	R	I	P	S
550	V	A	R	E	R	P	R	I	P	A
551	V	A	R	E	R	P	R	I	S	S
552	V	A	R	E	R	P	R	I	S	A
553	V	A	R	A	C	S	Q	V	P	A
554	V	A	R	A	C	S	Q	V	S	S
555	V	A	R	A	C	S	Q	V	S	A
556	V	A	R	A	C	S	Q	I	P	S
557	V	A	R	A	C	S	Q	I	P	A
558	V	A	R	A	C	S	Q	I	S	S
559	V	A	R	A	C	S	Q	I	S	A
560	V	A	R	A	C	S	R	V	P	A
561	V	A	R	A	C	S	R	V	S	S
562	V	A	R	A	C	S	R	V	S	A
563	V	A	R	A	C	S	R	I	P	S
564	V	A	R	A	C	S	R	I	P	A
565	V	A	R	A	C	S	R	I	S	S
566	V	A	R	A	C	S	R	I	S	A
567	V	A	R	A	C	P	Q	V	P	A
568	V	A	R	A	C	P	Q	V	S	S
569	V	A	R	A	C	P	Q	V	S	A
570	V	A	R	A	C	P	Q	I	P	S
571	V	A	R	A	C	P	Q	I	P	A
572	V	A	R	A	C	P	Q	I	S	S
573	V	A	R	A	C	P	Q	I	S	A
574	V	A	R	A	C	P	R	V	P	A
575	V	A	R	A	C	P	R	V	S	S
576	V	A	R	A	C	P	R	V	S	A
577	V	A	R	A	C	P	R	I	P	S
578	V	A	R	A	C	P	R	I	P	A
579	V	A	R	A	C	P	R	I	S	S
580	V	A	R	A	C	P	R	I	S	A
581	V	A	R	A	R	S	Q	V	P	A
582	V	A	R	A	R	S	Q	V	S	S
583	V	A	R	A	R	S	Q	V	S	A

Table2. Nov I Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
584	V	A	R	A	R	S	Q	I	P	S
585	V	A	R	A	R	S	Q	I	P	A
586	V	A	R	A	R	S	Q	I	S	S
587	V	A	R	A	R	S	Q	I	S	A
588	V	A	R	A	R	S	R	V	P	A
589	V	A	R	A	R	S	R	V	S	S
590	V	A	R	A	R	S	R	V	S	A
591	V	A	R	A	R	S	R	I	P	S
592	V	A	R	A	R	S	R	I	P	A
593	V	A	R	A	R	S	R	I	S	S
594	V	A	R	A	R	S	R	I	S	A
595	V	A	R	A	R	P	Q	V	P	A
596	V	A	R	A	R	P	Q	V	S	S
597	V	A	R	A	R	P	Q	V	S	A
598	V	A	R	A	R	P	Q	I	P	S
599	V	A	R	A	R	P	Q	I	P	A
600	V	A	R	A	R	P	Q	I	S	S
601	V	A	R	A	R	P	Q	I	S	A
602	V	A	R	A	R	P	R	V	P	A
603	V	A	R	A	R	P	R	V	S	S
604	V	A	R	A	R	P	R	V	S	A
605	V	A	R	A	R	P	R	I	P	S
606	V	A	R	A	R	P	R	I	P	A
607	V	A	R	A	R	P	R	I	S	S
608	V	A	R	A	R	P	R	I	S	A
609	V	A	H	E	C	S	Q	V	P	S
610	V	A	H	E	C	S	Q	V	P	A
611	V	A	H	E	C	S	Q	V	S	S
612	V	A	H	E	C	S	Q	V	S	A
613	V	A	H	E	C	S	Q	I	P	S
614	V	A	H	E	C	S	Q	I	P	A
615	V	A	H	E	C	S	Q	I	S	S
616	V	A	H	E	C	S	Q	I	S	A
617	V	A	H	E	C	S	R	V	P	S
618	V	A	H	E	C	S	R	V	P	A
619	V	A	H	E	C	S	R	V	S	S
620	V	A	H	E	C	S	R	V	S	A
621	V	A	H	E	C	S	R	I	P	S
622	V	A	H	E	C	S	R	I	P	A
623	V	A	H	E	C	S	R	I	S	S
624	V	A	H	E	C	S	R	I	S	A
625	V	A	H	E	C	P	Q	V	P	S
626	V	A	H	E	C	P	Q	V	P	A
627	V	A	H	E	C	P	Q	V	S	S
628	V	A	H	E	C	P	Q	V	S	A
629	V	A	H	E	C	P	Q	I	P	S
630	V	A	H	E	C	P	Q	I	P	A
631	V	A	H	E	C	P	Q	I	S	S
632	V	A	H	E	C	P	Q	I	S	A
633	V	A	H	E	C	P	R	V	P	S
634	V	A	H	E	C	P	R	V	P	A
635	V	A	H	E	C	P	R	V	S	S
636	V	A	H	E	C	P	R	V	S	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
637	V	A	H	E	C	P	R	I	P	S
638	V	A	H	E	C	P	R	I	P	A
639	V	A	H	E	C	P	R	I	S	S
640	V	A	H	E	C	P	R	I	S	A
641	V	A	H	E	R	S	Q	V	P	S
642	V	A	H	E	R	S	Q	V	P	A
643	V	A	H	E	R	S	Q	V	S	S
644	V	A	H	E	R	S	Q	V	S	A
645	V	A	H	E	R	S	Q	I	P	S
646	V	A	H	E	R	S	Q	I	P	A
647	V	A	H	E	R	S	Q	I	S	S
648	V	A	H	E	R	S	Q	I	S	A
649	V	A	H	E	R	S	R	V	P	S
650	V	A	H	E	R	S	R	V	P	A
651	V	A	H	E	R	S	R	V	S	S
652	V	A	H	E	R	S	R	V	S	A
653	V	A	H	E	R	S	R	I	P	S
654	V	A	H	E	R	S	R	I	P	A
655	V	A	H	E	R	S	R	I	S	S
656	V	A	H	E	R	S	R	I	S	A
657	V	A	H	E	R	P	Q	V	P	S
658	V	A	H	E	R	P	Q	V	P	A
659	V	A	H	E	R	P	Q	V	S	S
660	V	A	H	E	R	P	Q	V	S	A
661	V	A	H	E	R	P	Q	I	P	S
662	V	A	H	E	R	P	Q	I	P	A
663	V	A	H	E	R	P	Q	I	S	S
664	V	A	H	E	R	P	Q	I	S	A
665	V	A	H	E	R	P	R	V	P	S
666	V	A	H	E	R	P	R	V	P	A
667	V	A	H	E	R	P	R	V	S	S
668	V	A	H	E	R	P	R	V	S	A
669	V	A	H	E	R	P	R	I	P	S
670	V	A	H	E	R	P	R	I	P	A
671	V	A	H	E	R	P	R	I	S	S
672	V	A	H	E	R	P	R	I	S	A
673	V	A	H	A	C	S	Q	V	P	S
674	V	A	H	A	C	S	Q	V	P	A
675	V	A	H	A	C	S	Q	V	S	S
676	V	A	H	A	C	S	Q	V	S	A
677	V	A	H	A	C	S	Q	I	P	S
678	V	A	H	A	C	S	Q	I	P	A
679	V	A	H	A	C	S	Q	I	S	S
680	V	A	H	A	C	S	Q	I	S	A
681	V	A	H	A	C	S	R	V	P	S
682	V	A	H	A	C	S	R	V	P	A
683	V	A	H	A	C	S	R	V	S	S
684	V	A	H	A	C	S	R	V	S	A
685	V	A	H	A	C	S	R	I	P	S
686	V	A	H	A	C	S	R	I	P	A
687	V	A	H	A	C	S	R	I	S	S
688	V	A	H	A	C	S	R	I	S	A
689	V	A	H	A	C	P	Q	V	P	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
690	V	A	H	A	C	P	Q	V	P	A
691	V	A	H	A	C	P	Q	V	S	S
692	V	A	H	A	C	P	Q	V	S	A
693	V	A	H	A	C	P	Q	I	P	S
694	V	A	H	A	C	P	Q	I	P	A
695	V	A	H	A	C	P	Q	I	S	S
696	V	A	H	A	C	P	Q	I	S	A
697	V	A	H	A	C	P	R	V	P	S
698	V	A	H	A	C	P	R	V	P	A
699	V	A	H	A	C	P	R	V	S	S
700	V	A	H	A	C	P	R	V	S	A
701	V	A	H	A	C	P	R	I	P	S
702	V	A	H	A	C	P	R	I	P	A
703	V	A	H	A	C	P	R	I	S	S
704	V	A	H	A	C	P	R	I	S	A
705	V	A	H	A	R	S	Q	V	P	S
706	V	A	H	A	R	S	Q	V	P	A
707	V	A	H	A	R	S	Q	V	S	S
708	V	A	H	A	R	S	Q	V	S	A
709	V	A	H	A	R	S	Q	I	P	S
710	V	A	H	A	R	S	Q	I	P	A
711	V	A	H	A	R	S	Q	I	S	S
712	V	A	H	A	R	S	Q	I	S	A
713	V	A	H	A	R	S	R	V	P	S
714	V	A	H	A	R	S	R	V	P	A
715	V	A	H	A	R	S	R	V	S	S
716	V	A	H	A	R	S	R	V	S	A
717	V	A	H	A	R	S	R	I	P	S
718	V	A	H	A	R	S	R	I	P	A
719	V	A	H	A	R	S	R	I	S	S
720	V	A	H	A	R	S	R	I	S	A
721	V	A	H	A	R	P	Q	V	P	S
722	V	A	H	A	R	P	Q	V	P	A
723	V	A	H	A	R	P	Q	V	S	S
724	V	A	H	A	R	P	Q	V	S	A
725	V	A	H	A	R	P	Q	I	P	S
726	V	A	H	A	R	P	Q	I	P	A
727	V	A	H	A	R	P	Q	I	S	S
728	V	A	H	A	R	P	Q	I	S	A
729	V	A	H	A	R	P	R	V	P	S
730	V	A	H	A	R	P	R	V	P	A
731	V	A	H	A	R	P	R	V	S	S
732	V	A	H	A	R	P	R	V	S	A
733	V	A	H	A	R	P	R	I	P	S
734	V	A	H	A	R	P	R	I	P	A
735	V	A	H	A	R	P	R	I	S	S
736	V	A	H	A	R	P	R	I	S	A
737	V	T	R	E	C	S	Q	V	P	S
738	V	T	R	E	C	S	Q	V	P	A
739	V	T	R	E	C	S	Q	V	S	S
740	V	T	R	E	C	S	Q	V	S	A
741	V	T	R	E	C	S	Q	I	P	S
742	V	T	R	E	C	S	Q	I	P	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
743	V	T	R	E	C	S	Q	I	S	S
744	V	T	R	E	C	S	Q	I	S	A
745	V	T	R	E	C	S	R	V	P	S
746	V	T	R	E	C	S	R	V	P	A
747	V	T	R	E	C	S	R	V	S	S
748	V	T	R	E	C	S	R	V	S	A
749	V	T	R	E	C	S	R	I	P	S
750	V	T	R	E	C	S	R	I	P	A
751	V	T	R	E	C	S	R	I	S	S
752	V	T	R	E	C	S	R	I	S	A
753	V	T	R	E	C	P	Q	V	P	S
754	V	T	R	E	C	P	Q	V	P	A
755	V	T	R	E	C	P	Q	V	S	S
756	V	T	R	E	C	P	Q	V	S	A
757	V	T	R	E	C	P	Q	I	P	S
758	V	T	R	E	C	P	Q	I	P	A
759	V	T	R	E	C	P	Q	I	S	S
760	V	T	R	E	C	P	Q	I	S	A
761	V	T	R	E	C	P	R	V	P	S
762	V	T	R	E	C	P	R	V	P	A
763	V	T	R	E	C	P	R	V	S	S
764	V	T	R	E	C	P	R	V	S	A
765	V	T	R	E	C	P	R	I	P	S
766	V	T	R	E	C	P	R	I	P	A
767	V	T	R	E	C	P	R	I	S	S
768	V	T	R	E	C	P	R	I	S	A
769	V	T	R	E	R	S	Q	V	P	S
770	V	T	R	E	R	S	Q	V	P	A
771	V	T	R	E	R	S	Q	V	S	S
772	V	T	R	E	R	S	Q	V	S	A
773	V	T	R	E	R	S	Q	I	P	S
774	V	T	R	E	R	S	Q	I	P	A
775	V	T	R	E	R	S	Q	I	S	S
776	V	T	R	E	R	S	Q	I	S	A
777	V	T	R	E	R	S	R	V	P	S
778	V	T	R	E	R	S	R	V	P	A
779	V	T	R	E	R	S	R	V	S	S
780	V	T	R	E	R	S	R	V	S	A
781	V	T	R	E	R	S	R	I	P	S
782	V	T	R	E	R	S	R	I	P	A
783	V	T	R	E	R	S	R	I	S	S
784	V	T	R	E	R	S	R	I	S	A
785	V	T	R	E	R	P	Q	V	P	S
786	V	T	R	E	R	P	Q	V	P	A
787	V	T	R	E	R	P	Q	V	S	S
788	V	T	R	E	R	P	Q	V	S	A
789	V	T	R	E	R	P	Q	I	P	S
790	V	T	R	E	R	P	Q	I	P	A
791	V	T	R	E	R	P	Q	I	S	S
792	V	T	R	E	R	P	Q	I	S	A
793	V	T	R	E	R	P	R	V	P	S
794	V	T	R	E	R	P	R	V	P	A
795	V	T	R	E	R	P	R	V	S	S

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Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
796	V	T	R	E	R	P	R	V	S	A
797	V	T	R	E	R	P	R	I	P	S
798	V	T	R	E	R	P	R	I	P	A
799	V	T	R	E	R	P	R	I	S	S
800	V	T	R	E	R	P	R	I	S	A
801	V	T	R	A	C	S	Q	V	P	S
802	V	T	R	A	C	S	Q	V	P	A
803	V	T	R	A	C	S	Q	V	S	S
804	V	T	R	A	C	S	Q	V	S	A
805	V	T	R	A	C	S	Q	I	P	S
806	V	T	R	A	C	S	Q	I	P	A
807	V	T	R	A	C	S	Q	I	S	S
808	V	T	R	A	C	S	Q	I	S	A
809	V	T	R	A	C	S	R	V	P	S
810	V	T	R	A	C	S	R	V	P	A
811	V	T	R	A	C	S	R	V	S	S
812	V	T	R	A	C	S	R	V	S	A
813	V	T	R	A	C	S	R	I	P	S
814	V	T	R	A	C	S	R	I	P	A
815	V	T	R	A	C	S	R	I	S	S
816	V	T	R	A	C	S	R	I	S	A
817	V	T	R	A	C	P	Q	V	P	S
818	V	T	R	A	C	P	Q	V	P	A
819	V	T	R	A	C	P	Q	V	S	S
820	V	T	R	A	C	P	Q	V	S	A
821	V	T	R	A	C	P	Q	I	P	S
822	V	T	R	A	C	P	Q	I	P	A
823	V	T	R	A	C	P	Q	I	S	S
824	V	T	R	A	C	P	Q	I	S	A
825	V	T	R	A	C	P	R	V	P	S
826	V	T	R	A	C	P	R	V	P	A
827	V	T	R	A	C	P	R	V	S	S
828	V	T	R	A	C	P	R	V	S	A
829	V	T	R	A	C	P	R	I	P	S
830	V	T	R	A	C	P	R	I	P	A
831	V	T	R	A	C	P	R	I	S	S
832	V	T	R	A	C	P	R	I	S	A
833	V	T	R	A	R	S	Q	V	P	S
834	V	T	R	A	R	S	Q	V	P	A
835	V	T	R	A	R	S	Q	V	S	S
836	V	T	R	A	R	S	Q	V	S	A
837	V	T	R	A	R	S	Q	I	P	S
838	V	T	R	A	R	S	Q	I	P	A
839	V	T	R	A	R	S	Q	I	S	S
840	V	T	R	A	R	S	Q	I	S	A
841	V	T	R	A	R	S	R	V	P	S
842	V	T	R	A	R	S	R	V	P	A
843	V	T	R	A	R	S	R	V	S	S
844	V	T	R	A	R	S	R	V	S	A
845	V	T	R	A	R	S	R	I	P	S
846	V	T	R	A	R	S	R	I	P	A
847	V	T	R	A	R	S	R	I	S	S
848	V	T	R	A	R	S	R	I	S	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
849	V	T	R	A	R	P	Q	V	P	S
850	V	T	R	A	R	P	Q	V	P	A
851	V	T	R	A	R	P	Q	V	S	S
852	V	T	R	A	R	P	Q	V	S	A
853	V	T	R	A	R	P	Q	I	P	S
854	V	T	R	A	R	P	Q	I	P	A
855	V	T	R	A	R	P	Q	I	S	S
856	V	T	R	A	R	P	Q	I	S	A
857	V	T	R	A	R	P	R	V	P	S
858	V	T	R	A	R	P	R	V	P	A
859	V	T	R	A	R	P	R	V	S	S
860	V	T	R	A	R	P	R	V	S	A
861	V	T	R	A	R	P	R	I	P	S
862	V	T	R	A	R	P	R	I	P	A
863	V	T	R	A	R	P	R	I	S	S
864	V	T	R	A	R	P	R	I	S	A
865	V	T	H	E	C	S	Q	V	P	S
866	V	T	H	E	C	S	Q	V	P	A
867	V	T	H	E	C	S	Q	V	S	S
868	V	T	H	E	C	S	Q	V	S	A
869	V	T	H	E	C	S	Q	I	P	S
870	V	T	H	E	C	S	Q	I	P	A
871	V	T	H	E	C	S	Q	I	S	S
872	V	T	H	E	C	S	Q	I	S	A
873	V	T	H	E	C	S	R	V	P	S
874	V	T	H	E	C	S	R	V	P	A
875	V	T	H	E	C	S	R	V	S	S
876	V	T	H	E	C	S	R	V	S	A
877	V	T	H	E	C	S	R	I	P	S
878	V	T	H	E	C	S	R	I	P	A
879	V	T	H	E	C	S	R	I	S	S
880	V	T	H	E	C	S	R	I	S	A
881	V	T	H	E	C	P	Q	V	P	S
882	V	T	H	E	C	P	Q	V	P	A
883	V	T	H	E	C	P	Q	V	S	S
884	V	T	H	E	C	P	Q	V	S	A
885	V	T	H	E	C	P	Q	I	P	S
886	V	T	H	E	C	P	Q	I	P	A
887	V	T	H	E	C	P	Q	I	S	S
888	V	T	H	E	C	P	Q	I	S	A
889	V	T	H	E	C	P	R	V	P	S
890	V	T	H	E	C	P	R	V	P	A
891	V	T	H	E	C	P	R	V	S	S
892	V	T	H	E	C	P	R	V	S	A
893	V	T	H	E	C	P	R	I	P	S
894	V	T	H	E	C	P	R	I	P	A
895	V	T	H	E	C	P	R	I	S	S
896	V	T	H	E	C	P	R	I	S	A
897	V	T	H	E	R	S	Q	V	P	S
898	V	T	H	E	R	S	Q	V	P	A
899	V	T	H	E	R	S	Q	V	S	S
900	V	T	H	E	R	S	Q	V	S	A
901	V	T	H	E	R	S	Q	I	P	S

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Tabl 2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
902	V	T	H	E	R	S	Q	I	P	A
903	V	T	H	E	R	S	Q	I	S	S
904	V	T	H	E	R	S	Q	I	S	A
905	V	T	H	E	R	S	R	V	P	S
906	V	T	H	E	R	S	R	V	P	A
907	V	T	H	E	R	S	R	V	S	S
908	V	T	H	E	R	S	R	V	S	A
909	V	T	H	E	R	S	R	I	P	S
910	V	T	H	E	R	S	R	I	P	A
911	V	T	H	E	R	S	R	I	S	S
912	V	T	H	E	R	S	R	I	S	A
913	V	T	H	E	R	P	Q	V	P	S
914	V	T	H	E	R	P	Q	V	P	A
915	V	T	H	E	R	P	Q	V	S	S
916	V	T	H	E	R	P	Q	V	S	A
917	V	T	H	E	R	P	Q	I	P	S
918	V	T	H	E	R	P	Q	I	P	A
919	V	T	H	E	R	P	Q	I	S	S
920	V	T	H	E	R	P	Q	I	S	A
921	V	T	H	E	R	P	R	V	P	S
922	V	T	H	E	R	P	R	V	P	A
923	V	T	H	E	R	P	R	V	S	S
924	V	T	H	E	R	P	R	V	S	A
925	V	T	H	E	R	P	R	I	P	S
926	V	T	H	E	R	P	R	I	P	A
927	V	T	H	E	R	P	R	I	S	S
928	V	T	H	E	R	P	R	I	S	A
929	V	T	H	A	C	S	Q	V	P	S
930	V	T	H	A	C	S	Q	V	P	A
931	V	T	H	A	C	S	Q	V	S	S
932	V	T	H	A	C	S	Q	V	S	A
933	V	T	H	A	C	S	Q	I	P	S
934	V	T	H	A	C	S	Q	I	P	A
935	V	T	H	A	C	S	Q	I	S	S
936	V	T	H	A	C	S	Q	I	S	A
937	V	T	H	A	C	S	R	V	P	S
938	V	T	H	A	C	S	R	V	P	A
939	V	T	H	A	C	S	R	V	S	S
940	V	T	H	A	C	S	R	V	S	A
941	V	T	H	A	C	S	R	I	P	S
942	V	T	H	A	C	S	R	I	P	A
943	V	T	H	A	C	S	R	I	S	S
944	V	T	H	A	C	S	R	I	S	A
945	V	T	H	A	C	P	Q	V	P	S
946	V	T	H	A	C	P	Q	V	P	A
947	V	T	H	A	C	P	Q	V	S	S
948	V	T	H	A	C	P	Q	V	S	A
949	V	T	H	A	C	P	Q	I	P	S
950	V	T	H	A	C	P	Q	I	P	A
951	V	T	H	A	C	P	Q	I	S	S
952	V	T	H	A	C	P	Q	I	S	A
953	V	T	H	A	C	P	R	V	P	S
954	V	T	H	A	C	P	R	V	P	A

Table2. Novel Polymorphic Variant of IL4Rα (cont'd)

Polymorphic Variant Number	Amino Acid Position and Identities									
	75	82	185	400	431	503	576	579	675	752
955	V	T	H	A	C	P	R	V	S	S
956	V	T	H	A	C	P	R	V	S	A
957	V	T	H	A	C	P.	R	I	P	S
958	V	T	H	A	C	P	R	I	P	A
959	V	T	H	A	C	P	R	I	S	S
960	V	T	H	A	C	P	R	I	S	A
961	V	T	H	A	R	S	Q	V	P	S
962	V	T	H	A	R	S	Q	V	P	A
963	V	T	H	A	R	S	Q	V	S	S
964	V	T	H	A	R	S	Q	V	S	A
965	V	T	H	A	R	S	Q	I	P	S
966	V	T	H	A	R	S	Q	I	P	A
967	V	T	H	A	R	S	Q	I	S	S
968	V	T	H	A	R	S	Q	I	S	A
969	V	T	H	A	R	S	R	V	P	S
970	V	T	H	A	R	S	R	V	P	A
971	V	T	H	A	R	S	R	V	S	S
972	V	T	H	A	R	S	R	V	S	A
973	V	T	H	A	R	S	R	I	P	S
974	V	T	H	A	R	S	R	I	P	A
975	V	T	H	A	R	S	R	I	S	S
976	V	T	H	A	R	S	R	I	S	A
977	V	T	H	A	R	P	Q	V	P	S
978	V	T	H	A	R	P	Q	V	P	A
979	V	T	H	A	R	P	Q	V	S	S
980	V	T	H	A	R	P	Q	V	S	A
981	V	T	H	A	R	P	Q	I	P	S
982	V	T	H	A	R	P	Q	I	P	A
983	V	T	H	A	R	P	Q	I	S	S
984	V	T	H	A	R	P	Q	I	S	A
985	V	T	H	A	R	P	R	V	P	S
986	V	T	H	A	R	P	R	V	P	A
987	V	T	H	A	R	P	R	V	S	S
988	V	T	H	A	R	P	R	V	S	A
989	V	T	H	A	R	P	R	I	P	S
990	V	T	H	A	R	P	R	I	P	A
991	V	T	H	A	R	P	R	I	S	S
992	V	T	H	A	R	P	R	I	S	A

The invention also includes IL4Rα peptide variants, which are any fragments of an IL4Rα

protein variant that contains one or more of the amino acid variations shown in Table 2. An IL4Rα

peptide variant is at least 6 amino acids in length and is preferably any number between 6 and 30 amino

5 acids long, more preferably between 10 and 25, and most preferably between 15 and 20 amino acids long.

Such IL4Rα peptide variants may be useful as antigens to generate antibodies specific for one of the

above IL4Rα isoforms. In addition, the IL4Rα peptide variants may be useful in drug screening assays.

An IL4Rα variant protein or peptide of the invention may be prepared by chemical synthesis or

by expressing one of the variant IL4Rα genomic and cDNA sequences as described above. Alternatively,

10 the IL4Rα protein variant may be isolated from a biological sample of an individual having an IL4Rα

isogene which encodes the variant protein. Where the sample contains two different IL4Rα isoforms (i.e., the individual has different IL4Rα isogenes), a particular IL4Rα isoform of the invention can be isolated by immunoaffinity chromatography using an antibody which specifically binds to that particular IL4Rα isoform but does not bind to the other IL4Rα isoform.

5   The expressed or isolated IL4Rα protein may be detected by methods known in the art, including Coomassie blue staining, silver staining, and Western blot analysis using antibodies specific for the isoform of the IL4Rα protein as discussed further below. IL4Rα variant proteins can be purified by standard protein purification procedures known in the art, including differential precipitation, molecular sieve chromatography, ion-exchange chromatography, isoelectric focusing, gel electrophoresis, affinity

10   and immunoaffinity chromatography and the like. (Ausubel et. al., 1987, In Current Protocols in Molecular Biology John Wiley and Sons, New York, New York). In the case of immunoaffinity chromatography, antibodies specific for a particular polymorphic variant may be used..

        A polymorphic variant IL4Rα gene of the invention may also be fused in frame with a heterologous sequence to encode a chimeric IL4Rα protein. The non-IL4Rα portion of the chimeric

15   protein may be recognized by a commercially available antibody. In addition, the chimeric protein may also be engineered to contain a cleavage site located between the IL4Rα and non-IL4Rα portions so that the IL4Rα protein may be cleaved and purified away from the non-IL4Rα portion.

        An additional embodiment of the invention relates to using a novel IL4Rα protein isoform in any of a variety of drug screening assays. Such screening assays may be performed to identify agents that

20   bind specifically to all known IL4Rα protein isoforms or to only a subset of one or more of these isoforms. The agents may be from chemical compound libraries, peptide libraries and the like. The IL4Rα protein or peptide variant may be free in solution or affixed to a solid support. In one embodiment, high throughput screening of compounds for binding to an IL4Rα variant may be accomplished using the method described in PCT application WO84/03565, in which large numbers of

25   test compounds are synthesized on a solid substrate, such as plastic pins or some other surface, contacted with the IL4Rα protein(s) of interest and then washed. Bound IL4Rα protein(s) are then detected using methods well-known in the art.

        In another embodiment, a novel IL4Rα protein isoform may be used in assays to measure the binding affinities of one or more candidate drugs targeting the IL4Rα protein.

30   In another embodiment, the invention provides antibodies specific for and immunoreactive with one or more of the novel IL4Rα variant proteins described herein. The antibodies may be either monoclonal or polyclonal in origin. The IL4Rα protein or peptide variant used to generate the antibodies may be from natural or recombinant sources or produced by chemical synthesis using synthesis techniques known in the art. If the IL4Rα protein variant is of insufficient size to be antigenic, it may be

35   conjugated, complexed, or otherwise covalently linked to a carrier molecule to enhance the antigenicity of the peptide. Examples of carrier molecules, include, but are not limited to, albumins (e.g., human.

bovine, fish, ovine), and keyhole limpet hemocyanin (Basic and Clinical Immunology, 1991, Eds. D.P. Stites, and A.I. Terr, Appleton and Lange, Norwalk Connecticut, San Mateo, California).

        In one embodiment, an antibody specifically immunoreactive with one of the novel IL4Rα protein isoforms described herein is administered to an individual to neutralize activity of the IL4Rα

5   isoform expressed by that individual. The antibody may be formulated as a pharmaceutical composition which includes a pharmaceutically acceptable carrier.

        Antibodies specific for and immunoreactive with one of the novel IL4Rα protein isoform described herein may be used to immunoprecipitate the IL4Rα protein variant from solution as well as react with IL4Rα protein isoforms on Western or immunoblots of polyacrylamide gels on membrane

10   supports or substrates. In another preferred embodiment, the antibodies will detect IL4Rα protein isoforms in paraffin or frozen tissue sections, or in cells which have been fixed or unfixed and prepared on slides, coverslips, or the like, for use in immunocytochemical, immunohistochemical, and immunofluorescence techniques.

        In another embodiment, an antibody specifically immunoreactive with one of the novel IL4Rα

15   protein variants described herein is used in immunoassays to detect this variant in biological samples. In this method, an antibody of the present invention is contacted with a biological sample and the formation of a complex between the IL4Rα protein variant and the antibody is detected. As described, suitable immunoassays include radioimmunoassay, Western blot assay, immunofluorescent assay, enzyme linked immunoassay (ELISA), chemiluminescent assay, immunohistochemical assay, immunocytochemical

20   assay, and the like (see, e.g., Principles and Practice of Immunoassay, 1991, Eds. Christopher P. Price and David J. Neoman, Stockton Press, New York, New York; Current Protocols in Molecular Biology, 1987, Eds. Ausubel et al., John Wiley and Sons, New York, New York). Standard techniques known in the art for ELISA are described in Methods in Immunodiagnosis, 2nd Ed., Eds. Rose and Bigazzi, John Wiley and Sons, New York 1980; and Campbell et al., 1984, Methods in Immunology, W.A. Benjamin, Inc.).

25   Such assays may be direct, indirect, competitive, or noncompetitive as described in the art (see, e.g., Principles and Practice of Immunoassay, 1991, Eds. Christopher P. Price and David J. Neoman, Stockton Pres, NY, NY; and Oellirich, M., 1984, J. Clin. Chem. Clin. Biochem., 22:895-904). Proteins may be isolated from test specimens and biological samples by conventional methods, as described in Current Protocols in Molecular Biology, supra.

30   Exemplary antibody molecules for use in the detection and therapy methods of the present invention are intact immunoglobulin molecules, substantially intact immunoglobulin molecules, or those portions of immunoglobulin molecules that contain the antigen binding site. Polyclonal or monoclonal antibodies may be produced by methods conventionally known in the art (e.g., Kohler and Milstein, 1975, Nature, 256:495-497; Campbell Monoclonal Antibody Technology, the Production and

35   Characterization of Rodent and Human Hybridomas, 1985, In: Laboratory Techniques in Biochemistry and Molecular Biology, Eds. Burdon et al., Volume 13, Elsevier Science Publishers, Amsterdam). The

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antibodies or antigen binding fragments thereof may also be produced by genetic engineering. The technology for expression of both heavy and light chain genes in E. coli is the subject of PCT patent applications, publication number WO 901443, WO 901443 and WO 9014424 and in Huse et al., 1989, Science, 246:1275-1281. The antibodies may also be humanized (e.g., Queen, C. et al. 1989 Proc.

5   Natl. Acad. Sci. 86;10029).

Effect(s) of the polymorphisms identified herein on expression of IL4Rα may be investigated by preparing recombinant cells and/or organisms, preferably recombinant animals, containing a polymorphic variant of the IL4Rα gene. As used herein, "expression" includes but is not limited to one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor

10   mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into IL4Rα protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

To prepare a recombinant cell of the invention, the desired IL4Rα isogene may be introduced into the cell in a vector such that the isogene remains extrachromosomal. In such a situation, the gene will be

15   expressed by the cell from the extrachromosomal location. In a preferred embodiment, the IL4Rα isogene is introduced into a cell in such a way that it recombines with the endogenous IL4Rα gene present in the cell. Such recombination requires the occurrence of a double recombination event, thereby resulting in the desired IL4Rα gene polymorphism. Vectors for the introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector or

20   vector construct may be used in the invention. Methods such as electroporation, particle bombardment, calcium phosphate co-precipitation and viral transduction for introducing DNA into cells are known in the art; therefore, the choice of method may lie with the competence and preference of the skilled practitioner. Examples of cells into which the IL4Rα isogene may be introduced include, but are not limited to, continuous culture cells, such as COS, NIH/3T3, and primary or culture cells of the relevant

25   tissue type, i.e., they express the IL4Rα isogene. Such recombinant cells can be used to compare the biological activities of the different protein variants.

Recombinant organisms, i.e., transgenic animals, expressing a variant IL4Rα gene are prepared using standard procedures known in the art. Preferably, a construct comprising the variant gene is introduced into a nonhuman animal or an ancestor of the animal at an embryonic stage, i.e., the one-cell

30   stage, or generally not later than about the eight-cell stage. Transgenic animals carrying the constructs of the invention can be made by several methods known to those having skill in the art. One method involves transfecting into the embryo a retrovirus constructed to contain one or more insulator elements, a gene or genes of interest, and other components known to those skilled in the art to provide a complete shuttle vector harboring the insulated gene(s) as a transgene, see e.g., U.S. Patent No. 5,610,053. Another

35   method involves directly injecting a transgene into the embryo. A third method involves the use of embryonic stem cells. Examples of animals into which the IL4Rα isogenes may be introduced include,

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but are not limited to, mice, rats, other rodents, and nonhuman primates (see "The Introduction of Foreign Genes into Mice" and the cited references therein, In: Recombinant DNA, Eds. J.D. Watson, M. Gilman, J. Witkowski, and M. Zoller; W.H. Freeman and Company, New York, pages 254-272). Transgenic animals stably expressing a human IL4Rα isogene and producing human IL4Rα protein can be used as

5   biological models for studying diseases related to abnormal IL4Rα expression and/or activity, and for screening and assaying various candidate drugs, compounds, and treatment regimens to reduce the symptoms or effects of these diseases.

       An additional embodiment of the invention relates to pharmaceutical compositions for treating disorders affected by expression or function of a novel IL4Rα isogene described herein. The

10   pharmaceutical composition may comprise any of the following active ingredients: a polynucleotide comprising one of these novel IL4Rα isogenes; an antisense oligonucleotide directed against one of the novel IL4Rα isogenes, a polynucleotide encoding such an antisense oligonucleotide, or another compound which inhibits expression of a novel IL4Rα isogene described herein. Preferably, the composition contains the active ingredient in a therapeutically effective amount. By therapeutically

15   effective amount is meant that one or more of the symptoms relating to disorders affected by expression or function of a novel IL4Rα isogene is reduced and/or eliminated. The composition also comprises a pharmaceutically acceptable carrier, examples of which include, but are not limited to, saline, buffered saline, dextrose, and water. Those skilled in the art may employ a formulation most suitable for the active ingredient, whether it is a polynucleotide, oligonucleotide, protein, peptide or small molecule antagonist.

20   The pharmaceutical composition may be administered alone or in combination with at least one other agent, such as a stabilizing compound. Administration of the pharmaceutical composition may be by any number of routes including, but not limited to oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, intradermal, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal. Further details on techniques for formulation and

25   administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

       For any composition, determination of the therapeutically effective dose of active ingredient and/or the appropriate route of administration is well within the capability of those skilled in the art. For example, the dose can be estimated initially either in cell culture assays or in animal models. The animal

30   model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. The exact dosage will be determined by the practitioner, in light of factors relating to the patient requiring treatment, including but not limited to severity of the disease state, general health, age, weight and gender of the patient, diet, time and frequency of administration, other drugs being taken by the patient, and

35   tolerance/response to the treatment.

       Information on the identity of genotypes and haplotypes for the IL4Rα gene of any particular

individual as well as the frequency of such genotypes and haplotypes in any particular population of individuals is expected to be useful for a variety of basic research and clinical applications. Thus, the invention also provides compositions and methods for detecting the novel IL4Rα polymorphisms identified herein.

5   The compositions comprise at least one IL4Rα genotyping oligonucleotide. In one embodiment, an IL4Rα genotyping oligonucleotide is a probe or primer capable of hybridizing to a target region that is located close to, or that contains, one of the novel polymorphic sites described herein. As used herein, the term "oligonucleotide" refers to a polynucleotide molecule having less than about 100 nucleotides. A preferred oligonucleotide of the invention is 10 to 35 nucleotides long. More preferably, the

10   oligonucleotide is between 15 and 30, and most preferably, between 20 and 25 nucleotides in length. The oligonucleotide may be comprised of any phosphorylation state of ribonucleotides, deoxyribonucleotides, and acyclic nucleotide derivatives, and other functionally equivalent derivatives. Alternatively, oligonucleotides may have a phosphate-free backbone, which may be comprised of linkages such as carboxymethyl, acetamidate, carbamate, polyamide (peptide nucleic acid (PNA)) and the like (Varma, R.

15   in Molecular Biology and Biotechnology, A Comprehensive Desk Reference, Ed. R. Meyers, VCH Publishers, Inc. (1995), pages 617-620). Oligonucleotides of the invention may be prepared by chemical synthesis using any suitable methodology known in the art, or may be derived from a biological sample, for example, by restriction digestion. The oligonucleotides may be labeled, according to any technique known in the art, including use of radiolabels, fluorescent labels, enzymatic labels, proteins, haptens,

20   antibodies, sequence tags and the like.

          Genotyping oligonucleotides of the invention must be capable of specifically hybridizing to a target region of an IL4Rα polynucleotide, i.e., an IL4Rα isogene. As used herein, specific hybridization means the oligonucleotide forms an anti-parallel double-stranded structure with the target region under certain hybridizing conditions, while failing to form such a structure when incubated with a non-target

25   region or a non-IL4Rα polynucleotide under the same hybridizing conditions. Preferably, the oligonucleotide specifically hybridizes to the target region under conventional high stringency conditions. The skilled artisan can readily design and test oligonucleotide probes and primers suitable for detecting polymorphisms in the IL4Rα gene using the polymorphism information provided herein in conjunction with the known sequence information for the IL4Rα gene and routine techniques.

30   A nucleic acid molecule such as an oligonucleotide or polynucleotide is said to be a "perfect" or "complete" complement of another nucleic acid molecule if every nucleotide of one of the molecules is complementary to the nucleotide at the corresponding position of the other molecule. A nucleic acid molecule is "substantially complementary" to another molecule if it hybridizes to that molecule with sufficient stability to remain in a duplex form under conventional low-stringency conditions.

35   Conventional hybridization conditions are described, for example, by Sambrook J. et al., in Molecular Cloning, A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989)

and by Haymes, B.D. et al. in Nucleic Acid Hybridization, A Practical Appr ach, IRL Press, Washington, D.C. (1985). While perfectly complementary oligonucleotides are preferred for detecting polymorphisms, departures from complete complementarity are contemplated where such departures do not prevent the molecule from specifically hybridizing to the target region. For example, an

5   oligonucleotide primer may have a non-complementary fragment at its 5´ end, with the remainder of the primer being complementary to the target region. Alternatively, non-complementary nucleotides may be interspersed into the oligonucleotide probe or primer as long as the resulting probe or primer is still capable of specifically hybridizing to the target region.

Preferred genotyping oligonucleotides of the invention are allele-specific oligonucleotides. As

10   used herein, the term allele-specific oligonucleotide (ASO) means an oligonucleotide that is able, under sufficiently stringent conditions, to hybridize specifically to one allele of a gene, or other locus, at a target region containing a polymorphic site while not hybridizing to the corresponding region in another allele(s). As understood by the skilled artisan, allele-specificity will depend upon a variety of readily optimized stringency conditions, including salt and formamide concentrations, as well as temperatures for

15   both the hybridization and washing steps. Examples of hybridization and washing conditions typically used for ASO probes are found in Kogan et al., "Genetic Prediction of Hemophilia A" in PCR Protocols, A Guide to Methods and Applications, Academic Press, 1990 and Ruano et al., 87 Proc. Natl. Acad. Sci. USA 6296-6300, 1990. Typically, an allele-specific oligonucleotide will be perfectly complementary to one allele while containing a single mismatch for another allele.

20   Allele-specific oligonucleotide probes which usually provide good discrimination between different alleles are those in which a central position of the oligonucleotide probe aligns with the polymorphic site in the target region (e.g., approximately the 7th or 8th position in a 15 mer, the 8th or 9th position in a 16mer, the 10th or 11th position in a 20 mer). A preferred ASO probe for detecting IL4Rα gene polymorphisms comprises a nucleotide sequence, listed 5´ to 3´, selected from the group consisting

25   of:

    TTGCACCACTGCACT   (SEQ ID NO:4) and its complement,
    TTGCACCGCTGCACT   (SEQ ID NO:5) and its complement,

    TTTTGTGCTATTCCC   (SEQ ID NO:6) and its complement,
30 TTTTGTGTTATTCCC   (SEQ ID NO:7) and its complement,

    CTGGGCCGCTCAGGC   (SEQ ID NO:8) and its complement,
    CTGGGCCTCTCAGGC   (SEQ ID NO:9) and its complement,

35 TAAGCCTGCGCTGGA   (SEQ ID NO:10) and its complement,
    TAAGCCTCCGCTGGA   (SEQ ID NO:11) and its complement,

    AGAACAACGGAGGCG   (SEQ ID NO:12) and its complement,
    AGAACAATGGAGGCG   (SEQ ID NO:13) and its complement,
40
    CGGAGGCGCGGGGTG   (SEQ ID NO:14) and its complement,
    CGGAGGCACGGGGTG   (SEQ ID NO:15) and its complement,

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GTGCGGATAACTATA  (SEQ ID NO:16) and its complement,
GTGCGGACAACTATA  (SEQ ID NO:17) and its complement,

CGGAGTGCGGCAGGG  (SEQ ID NO:18) and its complement,
CGGAGTGTGGCAGGG  (SEQ ID NO:19) and its complement,

GCCTGGGCTGAGGGT  (SEQ ID NO:20) and its complement,
GCCTGGGTTGAGGGT  (SEQ ID NO:21) and its complement,

TGGGGTGGGCAGGGG  (SEQ ID NO:22) and its complement,
TGGGGTGAGCAGGGG  (SEQ ID NO:23) and its complement,

TTCTCCCGCAGTGAA  (SEQ ID NO:24) and its complement,
TTCTCCCACAGTGAA  (SEQ ID NO:25) and its complement,

GTGAAAACGACCCGG  (SEQ ID NO:26) and its complement,
GTGAAAATGACCCGG  (SEQ ID NO:27) and its complement,

GGCAAGCCCTGGGGC  (SEQ ID NO:28) and its complement,
GGCAAGCTCTGGGGC  (SEQ ID NO:29) and its complement,

GCCCTGGGGCTGGAT  (SEQ ID NO:30) and its complement,
GCCCTGGAGCTGGAT  (SEQ ID NO:31) and its complement,

ATAGCAAATCCCAGG  (SEQ ID NO:32) and its complement,
ATAGCAATTCCCAGG  (SEQ ID NO:33) and its complement,

GCTCTGCCCTAGGCA  (SEQ ID NO:34) and its complement,
GCTCTGCACTAGGCA  (SEQ ID NO:35) and its complement,

CCCCCACCCCTCACA  (SEQ ID NO:36) and its complement,
CCCCCACTCCTCACA  (SEQ ID NO:37) and its complement,

TCCCTCCGCATCGCA  (SEQ ID NO:38) and its complement,
TCCCTCCACATCGCA  (SEQ ID NO:39) and its complement,

CACCTGCTGTGGTGT  (SEQ ID NO:40) and its complement,
CACCTGCCGTGGTGT  (SEQ ID NO:41) and its complement,

ATGTCTGAAGTAGAC  (SEQ ID NO:42) and its complement,
ATGTCTGCAGTAGAC  (SEQ ID NO:43) and its complement,

TGACCAACCTTTGCT  (SEQ ID NO:44) and its complement,
TGACCAACTTTTGCT  (SEQ ID NO:45) and its complement,

CCTGTTTTCTGGAGC  (SEQ ID NO:46) and its complement,
CCTGTTTCCTGGAGC  (SEQ ID NO:47) and its complement,

TGGACCTGCTCGGAG  (SEQ ID NO:48) and its complement,
TGGACCTTCTCGGAG  (SEQ ID NO:49) and its complement,

AGTCATGCCTTCTTC  (SEQ ID NO:50) and its complement,
AGTCATGTCTTCTTC  (SEQ ID NO:51) and its complement,

GCCTTCTTCCACCTT  (SEQ ID NO:52) and its complement,
GCCTTCTCCCACCTT  (SEQ ID NO:53) and its complement,
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42

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          CAGCCCCCGTCTCGG (SEQ ID NO:54) and its complement,
          CAGCCCCTGTCTCGG (SEQ ID NO:55) and its complement,

          GGAGTTTGTACATGC (SEQ ID NO:56) and its complement,
5         GGAGTTTATACATGC (SEQ ID NO:57) and its complement,

          CAGCTCCCCAGAGCA (SEQ ID NO:58) and its complement,
          CAGCTCCTCAGAGCA (SEQ ID NO:59) and its complement,

10        AGACAGGTCCTCGCC (SEQ ID NO:60) and its complement,
          AGACAGGGCCTCGCC (SEQ ID NO:61) and its complement,

          CTGCCCCTGGCAATG (SEQ ID NO:62) and its complement,
          CTGCCCCCGGCAATG (SEQ ID NO:63) and its complement,
15
          AGGTGCATGTCCTCT (SEQ ID NO:64) and its complement,
          AGGTGCACGTCCTCT (SEQ ID NO:65) and its complement,

          GTGCATGTCCTCTTG (SEQ ID NO:66) and its complement,
20        GTGCATGCCCTCTTG (SEQ ID NO:67) and its complement,

          GGCTTATCCATGCCT (SEQ ID NO:68) and its complement,
          GGCTTATTCATGCCT (SEQ ID NO:69) and its complement,

25        AGCCAGGCTGGCAGA (SEQ ID NO:70) and its complement,
          AGCCAGGGTGGCAGA (SEQ ID NO:71) and its complement,

          GGCCCACATGGAGGC (SEQ ID NO:72) and its complement,
          GGCCCACGTGGAGGC (SEQ ID NO:73) and its complement,
30
          TAACACAGCCATCAA (SEQ ID NO:74) and its complement,
          TAACACAACCATCAA (SEQ ID NO:75) and its complement,

          TAATGCTCGTCTGTG (SEQ ID NO:76) and its complement,
35        TAATGCTTGTCTGTG (SEQ ID NO:77) and its complement,

          ACTTGCCGTCTGGGT (SEQ ID NO:78) and its complement, and
          ACTTGCCATCTGGGT (SEQ ID NO:79) and its complement.

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   An allele-specific oligonucleotide primer of the invention has a 3′ terminal nucleotide, or
preferably a 3′ penultimate nucleotide, that is complementary to only one nucleotide of a particular SNP,
thereby acting as a primer for polymerase-mediated extension only if the allele containing that nucleotide
is present. Allele-specific oligonucleotide primers hybridizing to either the coding or noncoding strand
45 are contemplated by the invention. A preferred ASO primer for detecting IL4Rα gene polymorphisms
comprises a nucleotide sequence, listed 5′ to 3′, selected from the group consisting of:

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      CTGAGATTGCACCAC (SEQ ID NO:80);  GGCTGGAGTGCAGTG (SEQ ID NO:81);
      CTGAGATTGCACCGC (SEQ ID NO:82);  GGCTGGAGTGCAGCG (SEQ ID NO:83);

50    CTGTGCTTTTGTGCT (SEQ ID NO:84);  ACCAAGGGGAATAGC (SEQ ID NO:85);
      CTGTGCTTTTGTGTT (SEQ ID NO:86);  ACCAAGGGGAATAAC (SEQ ID NO:87);
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GAGTTCCTGGGCCGC (SEQ ID NO:88); GGAGCAGCCTGAGCG (SEQ ID NO:89);
GAGTTCCTGGGCCTC (SEQ ID NO:90); GGAGCAGCCTGAGAG (SEQ ID NO:91);

TCCGAGTAAGCCTGC (SEQ ID NO:92); TCCAGCTCCAGCGCA (SEQ ID NO:93);
TCCGAGTAAGCCTCC (SEQ ID NO:94); TCCAGCTCCAGCGGA (SEQ ID NO:95);

TCCCTGAGAACAACG (SEQ ID NO:96); ACCCCGCGCCTCCGT (SEQ ID NO:97);
TCCCTGAGAACAATG (SEQ ID NO:98); ACCCCGCGCCTCCAT (SEQ ID NO:99);

GAACAACGGAGGCGC (SEQ ID NO:100); CACACGCACCCCGCG (SEQ ID NO:101);
GAACAACGGAGGCAC (SEQ ID NO:102); CACACGCACCCCGTG (SEQ ID NO:103);

TGGTCAGTGCGGATA (SEQ ID NO:104); CCAGTGTATAGTTAT (SEQ ID NO:105);
TGGTCAGTGCGGACA (SEQ ID NO:106); CCAGTGTATAGTTGT (SEQ ID NO:107);

GCAGGGCGGAGTGCG (SEQ ID NO:108); AGCCACCCCTGCCGC (SEQ ID NO:109);
GCAGGGCGGAGTGTG (SEQ ID NO:110); AGCCACCCCTGCCAC (SEQ ID NO:111);

ACAGCTGCCTGGGCT (SEQ ID NO:112); CACCCCACCCTCAGC (SEQ ID NO:113);
ACAGCTGCCTGGGTT (SEQ ID NO:114); CACCCCACCCTCAAC (SEQ ID NO:115);

TGAGGGTGGGGTGGG (SEQ ID NO:116); CCTCCTCCCCTGCCC (SEQ ID NO:117);
TGAGGGTGGGGTGAG (SEQ ID NO:118); CCTCCTCCCCTGCTC (SEQ ID NO:119);

GGCCGCTTCTCCCGC (SEQ ID NO:120); CTGGGTTTCACTGCG (SEQ ID NO:121);
GGCCGCTTCTCCCAC (SEQ ID NO:122); CTGGGTTTCACTGTG (SEQ ID NO:123);

TTTGGAGTGAAAACG (SEQ ID NO:124); CATCTGCCGGGTCGT (SEQ ID NO:125);
TTTGGAGTGAAAATG (SEQ ID NO:126); CATCTGCCGGGTCAT (SEQ ID NO:127);

CTGGGAGGCAAGCCC (SEQ ID NO:128); TATCCAGCCCCAGGG (SEQ ID NO:129);
CTGGGAGGCAAGCTC (SEQ ID NO:130); TATCCAGCCCCAGAG (SEQ ID NO:131);

AGGCAAGCCCTGGGG (SEQ ID NO:132); TTTGCTATCCAGCCC (SEQ ID NO:133);
AGGCAAGCCCTGGAG (SEQ ID NO:134); TTTGCTATCCAGCTC (SEQ ID NO:135);

GGCTGGATAGCAAAT (SEQ ID NO:136); CTAGCTCCTGGGATT (SEQ ID NO:137);
GGCTGGATAGCAATT (SEQ ID NO:138); CTAGCTCCTGGGAAT (SEQ ID NO:139);

CACCTGGCTCTGCCC (SEQ ID NO:140); GGGACTTGCCTAGGG (SEQ ID NO:141);
CACCTGGCTCTGCAC (SEQ ID NO:142); GGGACTTGCCTAGTG (SEQ ID NO:143);

CCTGGCCCCCCACCC (SEQ ID NO:144); CTCTGATGTGAGGGG (SEQ ID NO:145);
CCTGGCCCCCCACTC (SEQ ID NO:146); CTCTGATGTGAGGAG (SEQ ID NO:147);

GAACCCTCCCTCCGC (SEQ ID NO:148); GCTGGCTGCGATGCG (SEQ ID NO:149);
GAACCCTCCCTCCAC (SEQ ID NO:150); GCTGGCTGCGATGTG (SEQ ID NO:151);

TAGATACACCTGCTG (SEQ ID NO:152); GCAGATACACCACAG (SEQ ID NO:153);
TAGATACACCTGCCG (SEQ ID NO:154); GCAGATACACCACGG (SEQ ID NO:155);

GAAGGCATGTCTGAA (SEQ ID NO:156); ATGGCTGTCTACTTC (SEQ ID NO:157);
GAAGGCATGTCTGCA (SEQ ID NO:158); ATGGCTGTCTACTGC (SEQ ID NO:159);

GAACCCTGACCAACC (SEQ ID NO:160); TGCAAAAGCAAAGGA (SEQ ID NO:161);
GAACCCTGACCAATC (SEQ ID NO:162); TGCAAAAGCAAAGAA (SEQ ID NO:163);

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      TCTTGCCCTGTTTTC (SEQ ID NO:164);  TGTTGTGCTCCAGAA (SEQ ID NO:165);
      TCTTGCCCTGTTTCC (SEQ ID NO:166);  TGTTGTGCTCCAGGA (SEQ ID NO:167);

      TGTTCCTGGACCTGC (SEQ ID NO:168);  TCTCCTCTCCGAGCA (SEQ ID NO:169);
    5 TGTTCCTGGACCTTC (SEQ ID NO:170); TCTCCTCTCCGAGAA (SEQ ID NO:171);

      TGGGGGAGTCATGCC (SEQ ID NO:172);  AAGGTGGAAGAAGGC (SEQ ID NO:173);
      TGGGGGAGTCATGTC (SEQ ID NO:174);  AAGGTGGAAGAAGAC (SEQ ID NO:175);

   10 AGTCATGCCTTCTTC (SEQ ID NO:176);  TTCCCGAAGGTGGAA (SEQ ID NO:177);
      AGTCATGCCTTCTCC (SEQ ID NO:178);  TTCCCGAAGGTGGGA (SEQ ID NO:179);

      CAGCTGCAGCCCCCG (SEQ ID NO:180);  TGGGGGCCGAGACGG (SEQ ID NO:181);
      CAGCTGCAGCCCCTG (SEQ ID NO:182);  TGGGGGCCGAGACAG (SEQ ID NO:183);
   15
      CTATCAGGAGTTTGT (SEQ ID NO:184);  TCCACCGCATGTACA (SEQ ID NO:185);
      CTATCAGGAGTTTAT (SEQ ID NO:186);  TCCACCGCATGTATA (SEQ ID NO:187);

      CCCAAGCAGCTCCCC (SEQ ID NO:188);  CCCAGGTGCTCTGGG (SEQ ID, NO:189);
   20 CCCAAGCAGCTCCTC (SEQ ID NO:190);  CCCAGGTGCTCTGAG (SEQ ID NO:191);

      CTGTGGAGACAGGTC (SEQ ID NO:192); GTAGGGGGCGAGGAC (SEQ ID NO:193);
      CTGTGGAGACAGGGC (SEQ ID NO:194);  GTAGGGGGCGAGGCC (SEQ ID NO:195);

   25 TCCATCCTGCCCCTG (SEQ ID NO:196);  TCTGAGCATTGCCAG (SEQ ID NO:197);
      TCCATCCTGCCCCCG (SEQ ID NO:198);  TCTGAGCATTGCCGG (SEQ ID NO:199);

      TCTCTTAGGTGCATG (SEQ ID NO:200);  GCAACAAGAGGACAT (SEQ ID NO:201);
      TCTCTTAGGTGCACG (SEQ ID NO:202);  GCAACAAGAGGACGT (SEQ ID NO:203);
   30
      TCTTAGGTGCATGTC (SEQ ID NO:204);  CAGCAACAAGAGGAC (SEQ ID NO:205);
      TCTTAGGTGCATGCC (SEQ ID NO:206);  CAGCAACAAGAGGGC (SEQ ID NO:207);

      GACTAGGGCTTATCC (SEQ ID NO:208);  TTTCCCAGGCATGGA (SEQ ID NO:209);
   35 GACTAGGGCTTATTC (SEQ ID NO:210);  TTTCCCAGGCATGAA (SEQ ID NO:211);

      GAAGGCAGCCAGGCT (SEQ ID NO:212);  TGGAAATCTGCCAGC (SEQ ID NO:213);
      GAAGGCAGCCAGGGT (SEQ ID NO:214);  TGGAAATCTGCCACC (SEQ ID NO:215);

   40 GATCATGGCCCACAT (SEQ ID NO:216);  AGGTGGGCCTCCATG (SEQ ID NO:217);
      GATCATGGCCCACGT (SEQ ID NO:218);  AGGTGGGCCTCCACG (SEQ ID NO:219);

      AGAAACTAACACAGC (SEQ ID NO:220);  ATTCCCTTGATGGCT (SEQ ID NO:221);
      AGAAACTAACACAAC (SEQ ID NO:222);  ATTCCCTTGATGGTT (SEQ ID NO:223);
   45
      GTTGAGTAATGCTCG (SEQ ID NO:224);  AAAACACACAGACGA (SEQ ID NO:225);
      GTTGAGTAATGCTTG (SEQ ID NO:226);  AAAACACACAGACAA (SEQ ID NO:227);

      TAAGAAACTTGCCGT (SEQ ID NO:228);  ACCCAAACCCAGACG (SEQ ID NO:229);
   50 TAAGAAACTTGCCAT (SEQ ID NO:230); and ACCCAAACCCAGATG (SEQ ID NO:231).
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Other genotyping oligonucleotides of the invention hybridize to a target region located one to several nucleotides downstream of one of the novel polymorphic sites identified herein. Such oligonucleotides are useful in polymerase-mediated primer extension methods for detecting one of the

novel polymorphisms described herein and therefore such genotyping oligonucleotides are referred to herein as "primer-extension oligonucleotides". In a preferred embodiment, the 3′-terminus of a primer-extension oligonucleotide is a deoxynucleotide complementary to the nucleotide located immediately adjacent to the polymorphic site. A particularly preferred oligonucleotide primer for detecting IL4Rα gene polymorphisms by primer extension terminates in a nucleotide sequence, listed 5′ to 3′, selected from the group consisting of:

AGATTGCACC	(SEQ ID NO:232);	TGGAGTGCAG	(SEQ ID NO:233);
TGCTTTTGTG	(SEQ ID NO:234);	AAGGGGAATA	(SEQ ID NO:235);
TTCCTGGGCC	(SEQ ID NO:236);	GCAGCCTGAG	(SEQ ID NO:237);
GAGTAAGCCT	(SEQ ID NO:238);	AGCTCCAGCG	(SEQ ID NO:239);
CTGAGAACAA	(SEQ ID NO:240);	CCGCGCCTCC	(SEQ ID NO:241);
CAACGGAGGC	(SEQ ID NO:242);	ACGCACCCCG	(SEQ ID NO:243);
TCAGTGCGGA	(SEQ ID NO:244);	GTGTATAGTT	(SEQ ID NO:245);
GGGCGGAGTG	(SEQ ID NO:246);	CACCCCTGCC	(SEQ ID NO:247);
GCTGCCTGGG	(SEQ ID NO:248);	CCCACCCTCA	(SEQ ID NO:249);
GGGTGGGGTG	(SEQ ID NO:250);	CCTCCCCTGC	(SEQ ID NO:251);
CGCTTCTCCC	(SEQ ID NO:252);	GGTTTCACTG	(SEQ ID NO:253);
GGAGTGAAAA	(SEQ ID NO:254);	CTGCCGGGTC	(SEQ ID NO:255);
GGAGGCAAGC	(SEQ ID NO:256);	CCAGCCCCAG	(SEQ ID NO:257);
CAAGCCCTGG	(SEQ ID NO:258);	GCTATCCAGC	(SEQ ID NO:259);
TGGATAGCAA	(SEQ ID NO:260);	GCTCCTGGGA	(SEQ ID NO:261);
CTGGCTCTGC	(SEQ ID NO:262);	ACTTGCCTAG	(SEQ ID NO:263);
GGCCCCCCAC	(SEQ ID NO:264);	TGATGTGAGG	(SEQ ID NO:265);
CCCTCCCTCC	(SEQ ID NO:266);	GGCTGCGATG	(SEQ ID NO:267);
ATACACCTGC	(SEQ ID NO:268);	GATACACCAC	(SEQ ID NO:269);
GGCATGTCTG	(SEQ ID NO:270);	GCTGTCTACT	(SEQ ID NO:271);
CCCTGACCAA	(SEQ ID NO:272);	AAAAGCAAAG	(SEQ ID NO:273);
TGCCCTGTTT	(SEQ ID NO:274);	TGTGCTCCAG	(SEQ ID NO:275);
TCCTGGACCT	(SEQ ID NO:276);	CCTCTCCGAG	(SEQ ID NO:277);
GGGAGTCATG	(SEQ ID NO:278);	GTGGAAGAAG	(SEQ ID NO:279);
CATGCCTTCT	(SEQ ID NO:280);	CCGAAGGTGG	(SEQ ID NO:281);
CTGCAGCCCC	(SEQ ID NO:282);	GGGCCGAGAC	(SEQ ID NO:283);
TCAGGAGTTT	(SEQ ID NO:284);	ACCGCATGTA	(SEQ ID NO:285);
AAGCAGCTCC	(SEQ ID NO:286);	AGGTGCTCTG	(SEQ ID NO:287);
TGGAGACAGG	(SEQ ID NO:288);	GGGGGCGAGG	(SEQ ID NO:289);
ATCCTGCCCC	(SEQ ID NO:290);	GAGCATTGCC	(SEQ ID NO:291);
CTTAGGTGCA	(SEQ ID NO:292);	ACAAGAGGAC	(SEQ ID NO:293);

TAGGTGCATG	(SEQ ID NO:294);	CAACAAGAGG	(SEQ ID NO:295);
TAGGGCTTAT	(SEQ ID NO:296);	CCCAGGCATG	(SEQ ID NO:297);
GGCAGCCAGG	(SEQ ID NO:298);	AAATCTGCCA	(SEQ ID NO:299);
CATGGCCCAC	(SEQ ID NO:300);	TGGGCCTCCA	(SEQ ID NO:301);
AACTAACACA	(SEQ ID NO:302);	CCCTTGATGG	(SEQ ID NO:303);
GAGTAATGCT	(SEQ ID NO:304);	ACACACAGAC	(SEQ ID NO:305);
GAAACTTGCC	(SEQ ID NO:306); and CAAACCCAGA	(SEQ ID NO:307).

In some embodiments, a composition contains two or more differently labeled genotyping oligonucleotides for simultaneously probing the identity of nucleotides at two or more polymorphic sites. It is also contemplated that primer compositions may contain two or more sets of allele-specific primer pairs to allow simultaneous targeting and amplification of two or more regions containing a polymorphic site.

IL4Rα genotyping oligonucleotides of the invention may also be immobilized on or synthesized on a solid surface such as a microchip, bead, or glass slide (see, e.g., WO 98/20020 and WO 98/20019). Such immobilized genotyping oligonucleotides may be used in a variety of polymorphism detection assays, including but not limited to probe hybridization and polymerase extension assays. Immobilized IL4Rα genotyping oligonucleotides of the invention may comprise an ordered array of oligonucleotides designed to rapidly screen a DNA sample for polymorphisms in multiple genes at the same time.

In another embodiment, the invention provides a kit comprising at least two genotyping oligonucleotides packaged in separate containers. The kit may also contain other components such as hybridization buffer (where the oligonucleotides are to be used as a probe) packaged in a separate container. Alternatively, where the oligonucleotides are to be used to amplify a target region, the kit may contain, packaged in separate containers, a polymerase and a reaction buffer optimized for primer extension mediated by the polymerase, such as PCR.

The above described oligonucleotide compositions and kits are useful in methods for genotyping and/or haplotyping the IL4Rα gene in an individual. As used herein, the terms "IL4Rα genotype" and "IL4Rα haplotype" mean the genotype or haplotype contains the nucleotide pair or nucleotide, respectively, that is present at one or more of the novel polymorphic sites described herein and may optionally also include the nucleotide pair or nucleotide present at one or more additional polymorphic sites in the IL4Rα gene. The additional polymorphic sites may be currently known polymorphic sites or sites that are subsequently discovered.

One embodiment of the genotyping method involves isolating from the individual a nucleic acid mixture comprising the two copies of the IL4Rα gene, or a fragment thereof, that are present in the individual, and determining the identity of the nucleotide pair at one or more of the polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34. PS35. PS36.

PS37, PS38, PS39, PS40, PS41, PS44, and PS45 in th   two copies to assign an IL4Rα genotype to the individual. As will be readily understood by the skilled artisan, the two "copies" of a gene in an individual may be the same allele or may be different alleles. In a preferred embodiment of the genotyping method, the identity of the nucleotide pair at one or more of the polymorphic sites selected

. 5   from the group consisting of PS5, PS24, PS26, PS29, PS31, PS42, and PS43 is also determined. In a particularly preferred embodiment, the genotyping method comprises determining the identity of the nucleotide pair at each of PS1-45.

Typically, the nucleic acid mixture is isolated from a biological sample taken from the individual, such as a blood sample or tissue sample. Suitable tissue samples include whole blood, semen saliva,

10   tears, urine, fecal material, sweat, buccal, skin and hair. The nucleic acid mixture may be comprised of genomic DNA, mRNA, or cDNA and, in the latter two cases, the biological sample must be obtained . from an organ in which the IL4Rα gene is expressed. Furthermore it will be understood by the skilled artisan that mRNA or cDNA preparations would not be used to detect polymorphisms located in introns or in 5′ and 3′ nontranscribed regions. If an IL4Rα gene fragment is isolated, it must contain the

15   polymorphic site(s) to be genotyped.

One embodiment of the haplotyping method comprises isolating from the individual a nucleic acid molecule containing only one of the two copies of the IL4Rα gene, or a fragment thereof, that is present in the individual and determining in that copy the identity of the nucleotide at one or more of the polymorphic sites PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16,

20   PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45 in that copy to assign an IL4Rα haplotype to the individual. The nucleic acid may be isolated using any method capable of separating the two copies of the IL4Rα gene or fragment such as one of the methods described above for preparing IL4Rα isogenes, with targeted *in vivo* cloning being the preferred approach. As will be readily appreciated by those skilled

25   in the art, any individual clone will only provide haplotype information on one of the two IL4Rα gene copies present in an individual. If haplotype information is desired for the individual's other copy, additional IL4Rα clones will need to be examined. Typically, at least five clones should be examined to have more than a 90% probability of haplotyping both copies of the IL4Rα gene in an individual. In some embodiments, the haplotyping method also comprises identifying the nucleotide at one or more of

30   the polymorphic sites PS5, PS24, PS26, PS29, PS31, PS42, and PS43. In a particularly preferred embodiment, the nucleotide at each of PS1-45 is identified.

In a preferred embodiment, an IL4Rα haplotype pair is determined for an individual by identifying the phased sequence of nucleotides at one or more of the polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19,

35   PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45 in each copy of the IL4Rα gene that is present in the individual. In a

48

particularly preferred embodiment, the haplotyping method comprises identifying the phased sequenc of

nucleotides at each of PS1-45 in each copy of the IL4Rα gene. When haplotyping both copies of the

gene, the identifying step is preferably performed with each copy of the gene being placed in separate

containers. However, it is also envisioned that if the two copies are labeled with different tags, or are

5   otherwise separately distinguishable or identifiable, it could be possible in some cases to perform the

method in the same container. For example, if first and second copies of the gene are labeled with

different first and second fluorescent dyes, respectively, and an allele-specific oligonucleotide labeled

with yet a third different fluorescent dye is used to assay the polymorphic site(s), then detecting a

combination of the first and third dyes would identify the polymorphism in the first gene copy while

10   detecting a combination of the second and third dyes would identify the polymorphism in the second gene

copy.

In both the genotyping and haplotyping methods, the identity of a nucleotide (or nucleotide pair)

at a polymorphic site(s) may be determined by amplifying a target region(s) containing the polymorphic

site(s) directly from one or both copies of the IL4Rα gene, or fragment thereof, and the sequence of the

15   amplified region(s) determined by conventional methods. It will be readily appreciated by the skilled·

artisan that only one nucleotide will be detected at a polymorphic site in individuals who are homozygous

at that site, while two different nucleotides will be detected if the individual is heterozygous for that site.

The polymorphism may be identified directly, known as positive-type identification, or by inference,

referred to as negative-type identification. For example, where a SNP is known to be guanine and .

20   cytosine in a reference population, a site may be positively determined to be either guanine or cytosine for

an individual homozygous at that site, or both guanine and cytosine, if the individual is heterozygous at

that site. Alternatively, the site may be negatively determined to be not guanine (and thus

cytosine/cytosine) or not cytosine (and thus guanine/guanine).

In addition, the identity of the allele(s) present at any of the novel polymorphic sites described

25   herein may be indirectly determined by genotyping a polymorphic site not disclosed herein that is in

linkage disequilibrium with the polymorphic site that is of interest. Two sites are said to be in linkage

disequilibrium if the presence of a particular variant at one site enhances the predictability of another

variant at the second site (Stevens, JC 1999, *Mol. Diag.* 4: 309-17). Polymorphic sites in linkage

disequilibrium with the presently disclosed polymorphic sites may be located in regions of the gene or in

30   other genomic regions not examined herein. Genotyping of a polymorphic site in linkage disequilibrium

with the novel polymorphic sites described herein may be performed by, but is not limited to, any of the

above-mentioned methods for detecting the identity of the allele at a polymorphic site.

The target region(s) may be amplified using any oligonucleotide-directed amplification method,

including but not limited to polymerase chain reaction (PCR) (U.S. Patent No. 4,965,188), ligase chain

35   reaction (LCR) (Barany et al., Proc. Natl. Acad. Sci. USA 88:189-193, 1991; WO90/01069), and

oligonucleotide ligation assay (OLA) (Land gren et al., Science 241:1077-1080, 1988). Oligonucleotides

useful as prim rs or probes in such methods should specifically hybridize to a region of the nucleic acid

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that contains or is adjacent to the polymorphic site. Typically, the oligonucleotides are between 10 and 35 nucleotides in length and preferably, between 15 and 30 nucleotides in length. Most preferably, the oligonucleotides are 20 to 25 nucleotides long. The exact length of the oligonucleotide will depend on many factors that are routinely considered and practiced by the skilled artisan.

5   Other known nucleic acid amplification procedures may be used to amplify the target region including transcription-based amplification systems (U.S. Patent No. 5,130,238; EP 329,822; U.S. Patent No. 5,169,766, WO89/06700) and isothermal methods (Walker et al., *Proc. Natl. Acad. Sci. USA* **89**:392-396, 1992).

A polymorphism in the target region may also be assayed before or after amplification using one

10   of several hybridization-based methods known in the art. Typically, allele-specific oligonucleotides are utilized in performing such methods. The allele-specific oligonucleotides may be used as differently labeled probe pairs, with one member of the pair showing a perfect match to one variant of a target sequence and the other member showing a perfect match to a different variant. In some embodiments, more than one polymorphic site may be detected at once using a set of allele-specific oligonucleotides or

15   oligonucleotide pairs. Preferably, the members of the set have melting temperatures within 5°C, and more preferably within 2°C, of each other when hybridizing to each of the polymorphic sites being detected.

Hybridization of an allele-specific oligonucleotide to a target polynucleotide may be performed with both entities in solution, or such hybridization may be performed when either the oligonucleotide or

20   the target polynucleotide is covalently or noncovalently affixed to a solid support. Attachment may be mediated, for example, by antibody-antigen interactions, poly-L-Lys, streptavidin or avidin-biotin, salt bridges, hydrophobic interactions, chemical linkages, UV cross-linking baking, etc. Allele-specific oligonucleotides may be synthesized directly on the solid support or attached to the solid support subsequent to synthesis. Solid-supports suitable for use in detection methods of the invention include

25   substrates made of silicon, glass, plastic, paper and the like, which may be formed, for example, into wells (as in 96-well plates), slides, sheets, membranes, fibers, chips, dishes, and beads. The solid support may be treated, coated or derivatized to facilitate the immobilization of the allele-specific oligonucleotide or target nucleic acid.

The genotype or haplotype for the IL4Rα gene of an individual may also be determined by

30   hybridization of a nucleic sample containing one or both copies of the gene to nucleic acid arrays and subarrays such as described in WO 95/11995. The arrays would contain a battery of allele-specific oligonucleotides representing each of the polymorphic sites to be included in the genotype or haplotype.

The identity of polymorphisms may also be determined using a mismatch detection technique, including but not limited to the RNase protection method using riboprobes (Winter et al., Proc. Natl.

35   Acad. Sci. USA 82:7575, 1985; Meyers et al., Science 230:1242, 1985) and proteins which recognize nucleotide mismatches, such as the E. coli mutS protein (Modrich, P. Ann. Rev. Genet. 25:229-253, 1991). Alternatively, variant alleles can be identified by single strand conformation polymorphism

(SSCP) analysis (Orita et al., Genomics 5:874-879, 1989; Humphries et al., in Molecular Diagnosis of Genetic Diseases, R. Elles, ed., pp. 321-340, 1996) or denaturing gradient gel electrophoresis (DGGE) (Wartell et al., Nucl. Acids Res. 18:2699-2706, 1990; Sheffield et al., Proc. Natl. Acad. Sci. USA 86:232-236, 1989).

5   A polymerase-mediated primer extension method may also be used to identify the polymorphism(s). Several such methods have been described in the patent and scientific literature and include the "Genetic Bit Analysis" method (WO92/15712) and the ligase/polymerase mediated genetic bit analysis (U.S. Patent 5,679,524. Related methods are disclosed in WO91/02087, WO90/09455, WO95/17676, U.S. Patent Nos. 5,302,509, and 5,945,283. Extended primers containing a polymorphism

10   may be detected by mass spectrometry as described in U.S. Patent No. 5,605,798. Another primer extension method is allele-specific PCR (Ruaño et al., Nucl. Acids Res. 17:8392, 1989; Ruaño et al., Nucl. Acids Res. 19, 6877-6882, 1991; WO 93/22456; Turki et al., J. Clin. Invest. 95:1635-1641, 1995). In addition, multiple polymorphic sites may be investigated by simultaneously amplifying multiple regions of the nucleic acid using sets of allele-specific primers as described in Wallace et al.

15   (WO89/10414).

        In another aspect of the invention, an individual's IL4Rα haplotype pair is predicted from its IL4Rα genotype using information on haplotype pairs known to exist in a reference population. In its broadest embodiment, the haplotyping prediction method comprises identifying an IL4Rα genotype for the individual at two or more polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9,

20   PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45, enumerating all possible haplotype pairs which are consistent with the genotype, accessing data containing IL4Rα haplotype pairs identified in a reference population, and assigning a haplotype pair to the individual that is consistent with the data. In one embodiment, the reference haplotype pairs include

25   the IL4Rα haplotype pairs shown in Table 4.

        Generally, the reference population should be composed of randomly-selected individuals representing the major ethnogeographic groups of the world. A preferred reference population for use in the methods of the present invention comprises an approximately equal number of individuals from Caucasian, African American, Asian and Hispanic-Latino population groups with the minimum number

30   of each group being chosen based on how rare a haplotype one wants to be guaranteed to see. For example, if one wants to have a q% chance of not missing a haplotype that exists in the population at a p% frequency of occurring in the reference population, the number of individuals (n) who must be sampled is given by 2n=log(1-q)/log(1-p) where p and q are expressed as fractions. A preferred reference population allows the detection of any haplotype whose frequency is at least 10% with about 99%

35   certainty and comprises about 20 unrelated individuals from each of the four population groups named above. A particularly preferred reference population includes a 3-generation family representing one or more of the four population groups to serve as controls for checking quality of haplotyping procedures.

In a preferred embodiment, the haplotype frequency data for each ethnogeographic group is examined to determine whether it is consistent with Hardy-Weinberg equilibrium. Hardy-Weinberg equilibrium (D.L. Hartl et al., Principles of Population Genomics, Sinauer Associates (Sunderland, MA), 3rd Ed., 1997) postulates that the frequency of finding the haplotype pair H_1 / H_2 is equal to

5    $p_{H-W}(H_1 / H_2) = 2p(H_1)p(H_2)$ if $H_1 \neq H_2$ and $p_{H-W}(H_1 / H_2) = p(H_1)p(H_2)$ if $H_1 = H_2$. A statistically significant difference between the observed and expected haplotype frequencies could be due to one or more factors including significant inbreeding in the population group, strong selective pressure on the gene, sampling bias, and/or errors in the genotyping process. If large deviations from Hardy-Weinberg equilibrium are observed in an ethnogeographic group, the number of individuals in that group

10   can be increased to see if the deviation is due to a sampling bias. If a larger sample size does not reduce the difference between observed and expected haplotype pair frequencies, then one may wish to consider haplotyping the individual using a direct haplotyping method such as, for example, CLASPER System™ technology (U.S. Patent No. 5,866,404), SMD, or allele-specific long-range PCR (Michalotos-Beloin et al., Nucleic Acids Res. 24:4841-4843, 1996).

15   In one embodiment of this method for predicting an IL4Rα haplotype pair, the assigning step involves performing the following analysis. First, each of the possible haplotype pairs is compared to the haplotype pairs in the reference population. Generally, only one of the haplotype pairs in the reference population matches a possible haplotype pair and that pair is assigned to the individual. Occasionally, only one haplotype represented in the reference haplotype pairs is consistent with a possible haplotype

20   pair for an individual, and in such cases the individual is assigned a haplotype pair containing this known haplotype and a new haplotype derived by subtracting the known haplotype from the possible haplotype pair. In rare cases, either no haplotypes in the reference population are consistent with the possible haplotype pairs, or alternatively, multiple reference haplotype pairs are consistent with the possible haplotype pairs. In such cases, the individual is preferably haplotyped using a direct molecular

25   haplotyping method such as, for example, CLASPER System™ technology (U.S. Patent No. 5,866,404), SMD, or allele-specific long-range PCR (Michalotos-Beloin et al., Nucleic Acids Res. 24:4841-4843, 1996).

        The invention also provides a method for determining the frequency of an IL4Rα genotype or IL4Rα haplotype in a population. The method comprises determining the genotype or the haplotype pair

30   for the IL4Rα gene that is present in each member of the population, wherein the genotype or haplotype comprises the nucleotide pair or nucleotide detected at one or more of the polymorphic sites PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45 in the IL4Rα gene; and calculating the frequency any particular genotype or

35   haplotype is found in the population. The population may be a reference population, a family population, a same sex population, a population group, a trait population (e.g., a group of individuals exhibiting a trait

of interest such as a medical condition or response to a therapeutic treatment).

In another aspect of the invention, frequency data for IL4Rα genotypes and/or haplotypes found in a reference population are used in a method for identifying an association between a trait and an IL4Rα genotype or an IL4Rα haplotype. The trait may be any detectable phenotype, including but not limited to

5   susceptibility to a disease or response to a treatment. The method involves obtaining data on the frequency of the genotype(s) or haplotype(s) of interest in a reference population as well as in a population exhibiting the trait. Frequency data for one or both of the reference and trait populations may be obtained by genotyping or haplotyping each individual in the populations using one of the methods described above. The haplotypes for the trait population may be determined directly or, alternatively, by

10   the predictive genotype to haplotype approach described above. In another embodiment, the frequency data for the reference and/or trait populations is obtained by accessing previously determined frequency data, which may be in written or electronic form. For example, the frequency data may be present in a database that is accessible by a computer. Once the frequency data is obtained, the frequencies of the genotype(s) or haplotype(s) of interest in the reference and trait populations are compared. In a preferred

15   embodiment, the frequencies of all genotypes and/or haplotypes observed in the populations are compared. If a particular genotype or haplotype for the IL4Rα gene is more frequent in the trait population than in the reference population at a statistically significant amount, then the trait is predicted to be associated with that IL4Rα genotype or haplotype. Preferably, the IL4Rα genotype or haplotype being compared in the trait and reference populations is selected from the full-genotypes and full-

20   haplotypes shown in Tables 4 and 5, respectively, or from sub-genotypes and sub-haplotypes derived from these genotypes and haplotypes.

In a preferred embodiment of the method, the trait of interest is a clinical response exhibited by a patient to some therapeutic treatment, for example, response to a drug targeting IL4Rα or response to a therapeutic treatment for a medical condition. As used herein, "medical condition" includes but is not

25   limited to any condition or disease manifested as one or more physical and/or psychological symptoms for which treatment is desirable, and includes previously and newly identified diseases and other disorders. As used herein the term "clinical response" means any or all of the following: a quantitative measure of the response, no response, and adverse response (i.e., side effects).

In order to deduce a correlation between clinical response to a treatment and an IL4Rα genotype

30   or haplotype, it is necessary to obtain data on the clinical responses exhibited by a population of individuals who received the treatment, hereinafter the "clinical population". This clinical data may be obtained by analyzing the results of a clinical trial that has already been run and/or the clinical data may be obtained by designing and carrying out one or more new clinical trials. As used herein, the term "clinical trial" means any research study designed to collect clinical data on responses to a particular

35   treatment, and includes but is not limited to phase I, phase II and phase III clinical trials. Standard methods are used to define the patient population and to enroll subjects.

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It is preferred that the individuals included in the clinical population have been graded for the existence of the medical condition of interest. This is important in cases where the symptom(s) being presented by the patients can be caused by more than one underlying condition, and where treatment of the underlying conditions are not the same. An example of this would be where patients experience

5   breathing difficulties that are due to either asthma or respiratory infections. If both sets were treated with an asthma medication, there would be a spurious group of apparent non-responders that did not actually have asthma. These people would affect the ability to detect any correlation between haplotype and treatment outcome. This grading of potential patients could employ a standard physical exam or one or more lab tests. Alternatively, grading of patients could use haplotyping for situations where there is a

10 strong correlation between haplotype pair and disease susceptibility or severity.

The therapeutic treatment of interest is administered to each individual in the trial population and each individual's response to the treatment is measured using one or more predetermined criteria. It is contemplated that in many cases, the trial population will exhibit a range of responses and that the investigator will choose the number of responder groups (e.g., low, medium, high) made up by the

15 various responses. In addition, the IL4Rα gene for each individual in the trial population is genotyped and/or haplotyped, which may be done before or after administering the treatment.

After both the clinical and polymorphism data have been obtained, correlations between individual response and IL4Rα genotype or haplotype content are created. Correlations may be produced in several ways. In one method, individuals are grouped by their IL4Rα genotype or haplotype (or

20 haplotype pair) (also referred to as a polymorphism group), and then the averages and standard deviations of clinical responses exhibited by the members of each polymorphism group are calculated.

These results are then analyzed to determine if any observed variation in clinical response between polymorphism groups is statistically significant. Statistical analysis methods which may be used are described in L.D. Fisher and G. vanBelle, "Biostatistics: A Methodology for the Health Sciences",

25 Wiley-Interscience (New York) 1993. This analysis may also include a regression calculation of which polymorphic sites in the IL4Rα gene give the most significant contribution to the differences in phenotype. One regression model useful in the invention starts with a model of the form

$$r = r_0 + S \times d$$

where r is the response, r_0 is a constant called the "intercept", S is the slope and d is the dose. To

30 determine the dose, the most-common and least common nucleotides at the polymorphic site are first defined. Then, for each individual in the trial population, one calculates a "dose" as the number of least-common nucleotides the individual has at the polymorphic site of interest. This value can be 0 (homozygous for the least-common nucleotide), 1 (heterozygous), or 2 (homozygous for the most common nucleotide). An individual's "response" is the value of the clinical measurement. Standard

35 linear regression methods are then used to fit all the individuals' doses and responses to a single model (see e.g., L.D. Fisher and G. vanBelle, supra, Ch 9). The outputs of the regression calculation are the

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intercept r_0, the slope S, and the variance (which measures how well the data fits this simple linear model). The Students t-test value and the level of significance can then be calculated for each of the polymorphic sites.

A second method for finding correlations between IL4Rα haplotype content and clinical responses uses predictive models based on error-minimizing optimization algorithms. One of many possible optimization algorithms is a genetic algorithm (R. Judson, "Genetic Algorithms and Their Uses in Chemistry" in Reviews in Computational Chemistry, Vol. 10, pp. 1-73, K. B. Lipkowitz and D. B. Boyd, eds. (VCH Publishers, New York, 1997). Simulated annealing (Press et al., "Numerical Recipes in C: The Art of Scientific Computing", Cambridge University Press (Cambridge) 1992, Ch. 10), neural networks (E. Rich and K. Knight, "Artificial Intelligence", 2nd Edition (McGraw-Hill, New York, 1991, Ch. 18), standard gradient descent methods (Press et al., supra Ch. 10), or other global or local optimization approaches (see discussion in Judson, supra) could also be used. As an example, a genetic algorithm approach is described herein. This method searches for optimal parameters or weights in linear or non-linear models connecting IL4Rα haplotype loci and clinical outcome. One model is of the form

$$C = C_0 + \sum_\alpha \left(\sum_i w_{i,\alpha} R_{i,\alpha} + \sum_i w'_{i,\alpha} L_{i,\alpha} \right) \qquad [1]$$

where C is the measured clinical outcome, i goes over all polymorphic sites, α over all candidate genes, C_0, $w_{i,\alpha}$ and $w'_{i,\alpha}$ are variable weight values, $R_{i,\alpha}$ is equal to 1 if site i in gene α in the first haplotype takes on the most common nucleotide and −1 if it takes on the less common nucleotide. $L_{i,\alpha}$ is the same as $R_{i,\alpha}$ except for the second haplotype. The constant term C_0 and the weights $w_{i,\alpha}$ and $w'_{i,\alpha}$ are varied by the genetic algorithm during a search process that minimizes the error between the measured value of C and the value calculated from Equation 1. Models other than the one given in Equation 1 can be readily incorporated by those skilled in the art for analyzing the clinical and polymorphism data. The genetic algorithm is especially suited for searching not only over the space of weights in a particular model but also over the space of possible models (Judson, supra).

Correlations may also be analyzed using analysis of variation (ANOVA) techniques to determine how much of the variation in the clinical data is explained by different subsets of the polymorphic sites in the IL4Rα gene. ANOVA is used to test hypotheses about whether a response variable is caused by or correlated with one or more traits or variables that can be measured (Fisher and vanBelle, supra, Ch. 10). These traits or variables are called the independent variables. To carry out ANOVA, the independent variable(s) are measured and individuals are placed into groups based on their values for these variables. In this case, the independent variable(s) refers to the combination of polymorphisms present at a subset of the polymorphic sites, and thus, each group contains those individuals with a given genotype or haplotype pair. The variation in response within the groups and also the variation between groups is then measured. If the within-group response variation is large (people in a group have a wide range of responses) and the

response variation between groups is small (the average responses for all groups are about the same) then it can be concluded that the independent variables used for the grouping are not causing or correlated with the response variable. For instance, if people are grouped by month of birth (which should have nothing to do with their response to a drug) the ANOVA calculation should show a low level of significance.

5   However, if the response variation is larger between groups than within groups, the F-ratio (="between groups" divided by "within groups") is greater than one. Large values of the F-ratio indicate that the independent variable is causing or correlated with the response. The calculated F-ratio is preferably compared with the critical F-distribution value at whatever level of significance is of interest. If the F-ratio is greater than the Critical F-distribution value, then one may be confident that the individual's

10   genotype or haplotype pair for this particular subset of polymorphic sites in the IL4Rα gene is at least partially responsible for, or is at least strongly correlated with the clinical response.

From the analyses described above, a mathematical model may be readily constructed by the skilled artisan that predicts clinical response as a function of IL4Rα genotype or haplotype content. Preferably, the model is validated in one or more follow-up clinical trials designed to test the model.

15   The identification of an association between a clinical response and a genotype or haplotype (or haplotype pair) for the IL4Rα gene may be the basis for designing a diagnostic method to determine those individuals who will or will not respond to the treatment, or alternatively, will respond at a lower level and thus may require more treatment, i.e., a greater dose of a drug. The diagnostic method may take one of several forms: for example, a direct DNA test (i.e., genotyping or haplotyping one or more of the

20   polymorphic sites in the IL4Rα gene), a serological test, or a physical exam measurement. The only requirement is that there be a good correlation between the diagnostic test results and the underlying IL4Rα genotype or haplotype that is in turn correlated with the clinical response. In a preferred embodiment, this diagnostic method uses the predictive haplotyping method described above.

Any or all analytical and mathematical operations involved in practicing the methods of the

25   present invention may be implemented by a computer. In addition, the computer may execute a program that generates views (or screens) displayed on a display device and with which the user can interact to view and analyze large amounts of information relating to the IL4Rα gene and its genomic variation, including chromosome location, gene structure, and gene family, gene expression data, polymorphism data, genetic sequence data, and clinical data population data (e.g., data on ethnogeographic origin,

30   clinical responses, genotypes, and haplotypes for one or more populations). The IL4Rα polymorphism data described herein may be stored as part of a relational database (e.g., an instance of an Oracle database or a set of ASCII flat files). These polymorphism data may be stored on the computer's hard drive or may, for example, be stored on a CD ROM or on one or more other storage devices accessible by the computer. For example, the data may be stored on one or more databases in communication with the

35   computer via a network.

Preferred embodiments of the invention are described in the following examples. Other

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embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples.

5

EXAMPLES

The Examples herein are meant to exemplify the various aspects of carrying out the invention and are not intended to limit the scope of the invention in any way. The Examples do not include detailed descriptions for conventional methods employed, such as in the performance of genomic DNA isolation,

10   PCR and sequencing procedures. Such methods are well-known to those skilled in the art and are described in numerous publications, for example, Sambrook, Fritsch, and Maniatis, "Molecular Cloning: A Laboratory Manual", 2nd Edition, Cold Spring Harbor Laboratory Press, USA, (1989).

15 -

Example 1A

This example illustrates examination of various regions of the IL4Rα gene for polymorphic sites using DNA from Index Repository IA.

Amplification of Target Regions

20   The following target regions of the IL4Rα gene were amplified using the PCR primer pairs listed below, with the sequences presented in the 5′ to 3′ direction and nucleotide positions shown for each region corresponding to the indicated GenBank Accession No.

Accession Number: AC004525
Fragment 1
25   Forward Primer
32801-32822   CCACAGTCATCCCGACACTAGC (SEQ ID NO:308)
Reverse Primer
Complement of 33355-33334   TATTCCAGCCGTATCCATGTGC (SEQ ID NO:309)
PCR product 555 nt

30
Fragment 2
Forward Primer
35515-35536   CCTTGGTGCATGTGGTAAGAGG (SEQ ID NO:310)
Reverse Primer
35   Complement of 36068-36046   TTTCAAAGGTGGGAGGACTGAGG (SEQ ID NO:311)
PCR product 554 nt

Fragment 3
Forward Primer
40   37031-37050   GCAGTGAGCTGGGATTGTGC (SEQ ID NO:312)
Reverse Primer
Complement of 37701-37679   AACTCCCCTTCTCTGATGTGAGG (SEQ ID NO:313)
PCR product 671 nt

Fragment 4
Forward Primer
43240-43262   TCACAGTTACAGAGGTGGCAAGC (SEQ ID NO:314)
Reverse Primer
5   Complement of 43727-43706   CTGCCTACCTGGCAGATACACC (SEQ ID NO:315)
PCR product 488 nt

Fragment 5
Forward Primer
10   49553-49574. AGCTGTCACTCCACCTCCTTGG (SEQ ID NO:316)
Reverse Primer
Complement of 50036-50013   AAAGCCTCTGGTCTGCTAATGACC (SEQ ID NO:317)
PCR product 484 nt

15   Fragment 6
Forward Primer
51394-51415   GGGAGGAGATTCAGAGCACTCC (SEQ ID NO:318)
Reverse Primer
Complement of 51847-51826   CAGTCCACGTTTCCAGAACACC (SEQ ID NO:319)
20   PCR product 454 nt

Fragment 7
Forward Primer
52806-52826   GGCTTGGGATAATGGTGTTGC (SEQ ID NO:320)
25   Reverse Primer
Complement of 53529-53507   TACTTCCCGAAGGTGGAAGAAGG (SEQ ID NO:321)
PCR product 724 nt

Fragment 8
30   Forward Primer
53242-53265   CAGTGGAGATCAGCAAGACAGTCC (SEQ ID NO:322)
Reverse Primer
Complement of 53807-53786   GGGCATCTCGGGTTCTACTTCC (SEQ ID NO:323)
PCR product 566 nt

35
Fragment 9
Forward Primer
53522-53544   GGGAAGTACGAGTGCTCACATGC (SEQ ID NO:324)
Reverse Primer
40   Complement of 54110-54088   CTTATACCCCTCTTCCCCACTGC (SEQ ID NO:325)
PCR product 589 nt

Fragment 10
Forward Primer
45   53821-53841   TCTCTGAGCCAACCACTGTGC (SEQ ID NO:326)
Reverse Primer
Complement of 54359-54337   GGCTGAGTAGACAATGCCACTGC (SEQ ID NO:327)
PCR product 539 nt

50   Fragment 11
Forward Primer
54055-54076   CTGTGTCCCCAGAGAAATGTGG (SEQ ID NO:328)
Reverse Primer
Complement of 54717-54695   GACTCAGCAACAAGAGGACATGC (SEQ ID NO:329)
55   PCR product 663 nt

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Fragment 12
Forward Primer
54342-54365   GGCATTGTCTACTCAGCCCTTACC (SEQ ID NO:330)
Reverse Primer
5   Complement of 54986-54967   ACAAGTCGAGGTGCCCAAGG (SEQ ID NO:331)
PCR product 645 nt

Fragment 13
Forward Primer
10   54669-54693   CCCACATACATGAGGGTCTCTTAGG (SEQ ID NO:332)
Reverse Primer
Complement of 55270-55250   ATTCTGCCTCCAGCATCAACC (SEQ ID NO:333)
PCR product 602 nt

15   Fragment 14
Forward Primer
55235-55258   AACAGAGCTTCCTTAGGTTGATGC (SEQ ID NO:334)
Reverse Primer
Complement of 55847-55825   CCTCAGTTCCCCACTACCTTAGC (SEQ ID NO:335)
20   PCR product 613 nt

These primer pairs were used in PCR reactions containing genomic DNA isolated from
immortalized cell lines for each member of Index Repository IA. The PCR reactions were carried out
under the following conditions:

25   Reaction volume   = 20 μl
10 x Advantage 2 Polymerase reaction buffer (Clontech)   = 2 μl
100 ng of human genomic DNA   = 1 μl
10 mM dNTP   = 0.4 μl
Advantage 2 Polymerase enzyme mix (Clontech)   = 0.2 μl
30   Forward Primer (10 μM)   = 0.4 μl
Reverse Primer (10 μM)   = 0.4 μl
Water   =15.6μl

Amplification profile:
35   94°C - 2 min.   1 cycle

· 94°C - 30 sec.
70°C - 45 sec.   } 10 cycles
72°C - 1 min.
40

94°C - 30 sec.
64°C - 45 sec.   } 35 cycles
72°C - 1 min.

45   Sequencing of PCR Products

The PCR products were purified by Solid Phase Reversible Immobilization using the protocol
developed by the Whitehead Genome Center. A detailed protocol can be found at
http://www.genome.wi.mit.edu/sequencing/protocols/pure/SPRI_pcr.html.

Briefly, five μl of carboxyl coated magnetic beads (10 mg/ml) and 60 μl of HYB BUFFER (2.5M

NaCl/20% PEG 8000) were added to each PCR reaction mixture (20 µl). The reaction mixture was mixed well and incubated at room temperature (RT) for 10 min. The microtitre plate was placed on a magnet for 2 min and the beads washed twice with 150 µl of 70% EtOH. The beads were air dried for 2 min and the DNA was eluted in 25 µl of distilled water and incubated at RT for 5 min. The beads were

5   magnetically separated and the supernatant removed for testing and sequencing.

The purified PCR products were sequenced in both directions using the primer sets described previously or those listed, in the 5′ to 3′ direction, below.

Accession Number: AC004525
Fragment 1

10   Forward Primer
32865-32882   GCGCTGGCCCTCAACTTT (SEQ ID NO:336)
Reverse Primer
Complement of 33283-33264   GTCCCTGGAGATGGGACCTC (SEQ ID NO:337)

15   Fragment 2
Forward Primer
35598-35617   GCCCCCAGATCTGTCCTCAC (SEQ ID NO:338)
Reverse Primer
Complement of 36013-35994   GGAAAATACAGGCGGCTTCC (SEQ ID NO:339)

20   Fragment 3
Forward Primer
37182-37203   GGCTCTGAATCTGTGTGGTGCT (SEQ ID NO:340)
Reverse Primer

25   Complement of 37639-37620   AGCCAGGTGAGAAGCCAGGT (SEQ ID NO:341)

Fragment 4
Forward Primer
43266-43285   GGCCTGAACAGGACGAACAA (SEQ ID NO:342)

30   Reverse Primer
Complement of 43687-43668   GGCAGGATTGCCATTAGAGG (SEQ ID NO:343)

Fragment 5
Forward Primer

35   49639-49660   TGAGTCAGTGGTTTGACCTCCA (SEQ ID NO:344)
Reverse Primer
Complement of 49999-49980   GCCTCTGTCTCCCCTGCAAC (SEQ ID NO:345)

Fragment 6

40   Forward Primer
51423-51442   CCACTTTTGCCATCGACCAC (SEQ ID NO:346)
Reverse Primer
Complement of 51818-51799   CTGCCGTCCCTTGAAGGCTA (SEQ ID NO:347)

45   Fragment 7
Forward Primer
52932-52953   CCCTACCCTCAGGGATTTCTCA (SEQ ID NO:348)
Reverse Primer
Complement of 53474-53455   CCCATTCTCCTCTCCGAGCA (SEQ ID NO:349)

50

Fragment 8
Forward Primer
53280-53299   ATCAGCGTGGTGCGATGTGT (SEQ ID NO:350)
Reverse Primer
5   Complement of 53756-53737   ACCCAGCTCTCTGGGACACG (SEQ ID NO:351)

Fragment 9
Forward Primer
53548-53568   GGGATGAGTTCCCAAGTGCAG (SEQ ID NO:352)
10   Reverse Primer
Complement of 54048-54029   TGGCAAGCAGGCTTGAGAAG (SEQ ID NO:353)

Fragment 10
Forward Primer
15   53841-53860   CCCCAACCTGAGCCAGAAAC (SEQ ID NO:354)
Reverse Primer
Complement of 54330-54311   TGTCCACAAGGGGGTCTGTG (SEQ ID NO:355)

Fragment 11
20   Forward Primer
54083-54102   GGCTAGCAGTGGGGAAGAGG (SEQ ID NO:356)
Reverse Primer
Complement of 54617-54600   ATTGCCAGGGGCAGGATG (SEQ ID NO:357)

25   Fragment 12
Forward Primer
54422-54441   CCCTGTCATGGCCAGTCCTT (SEQ ID NO:358)
Reverse Primer
Complement of 54929-54910   GCGACCCAGTGCCCTCTACT (SEQ ID NO:359)
30
Fragment 13
Forward Primer
54694-54715   TGCATGTCCTCTTGTTGCTGAG (SEQ ID NO:360)
Reverse Primer
35   Complement of 55213-55194   CAATGACCACCCTCCCTGAA (SEQ ID NO:361)

Fragment 14
Forward Primer
55273-55291   CGGCTGTCAAGGGGTGTTC (SEQ ID NO:362)
40   Reverse Primer
Complement of 55769-55750   CCAAACCCAGACGGCAAGTT (SEQ ID NO:363)

45   <u>Analysis of Sequences for Polymorphic Sites</u>
        Sequences were analyzed for the presence of polymorphisms using the Polyphred program
(Nickerson et al., Nucleic Acids Res. 14:2745-2751, 1997). The presence of a polymorphism was
confirmed on both strands. The polymorphisms and their locations in the IL4Rα gene are listed in Table
3 below.

50   <u>Example 1B</u>
        This example illustrates examination of the IL4Rα gene for polymorphic sites in the following

target regions: 1000 base pairs upstream of the ATG start codon; each of the exons, including

approximately 100 base pairs on either side of the exon; and 500-1000 base paris downstream of the

termination codon.

5   Amplification of the Target Regions

PCR primers, which were designed based on the nearly complete IL4R genomic sequence

reported in the GenBank database (Accession No: AC004525), are set forth below:

Promoter
Forward Primer
10   30094-30117   AAACCCCTGGACTCCAAGTGATCC (SEQ ID NO:364)
Reverse Primer
Complement of 30842-30819   AAGCGATTCTTCTGCCTCAGCCTC (SEQ ID NO:365)
PCR product 749 nt

15   Exon 1
Forward Primer
30517-30540   GGACAGTTGTTGTGTAGCTCACCC (SEQ ID NO:366)
Reverse Primer
Complement of 31409-31431   CTATGTTGCCCAAGCTGACCTC (SEQ ID NO:367)
20   PCR product 893 nt

Exon 2
Forward Primer
32871-32890   GCCCTCAACTTTGCCTGCAC (SEQ ID NO:368)
25   Reverse Primer
Complement of 33362-33340   AGTCCAGTATTCCAGCCGTATCC (SEQ ID NO:369)
PCR product 492 nt

Exon 3
30   Forward Primer
35623-35644   TGATCGGGAAGCTGGAAGAGTC (SEQ ID NO:370)
Reverse Primer
Complement of 36070-36049   CGTTTCAAAGGTGGGAGGACTG (SEQ ID NO:371)
PCR product 448 nt
35
Exon 4
Forward Primer
37230-37250   CGACCAAAAATCTGGGTGGTG (SEQ ID NO:372)
Reverse Primer
40   Complement of 37668-37648   CAGGAAGCAAAGGGACTTGCC (SEQ ID NO:373)
PCR product 439 nt

Exon 5
Forward Primer
45   43307-43328   TCTTAAACATGGTGGGGTCAGC (SEQ ID NO:374)
Reverse Primer
Complement of 43765-43745   CATGGAAATTGTGGGCTTGTG (SEQ ID NO:375)
PCR product 459 nt

50   Exon 6
Forward Primer
46507-46528   ATGTGCAAGAGGGAGAGTGGTG (SEQ ID NO:376)

Reverse Primer
Complem nt of 46870-46849   TGACTGAGAGGACTGCAAAGGG (SEQ ID NO:377)
PCR product 364 nt

5   Exon 7
Forward Primer
· 49672-49695   GCCTGATCTCTGATGCCAAATAAG (SEQ ID NO:378) .
Reverse Primer
· Complement of 49964-49983   TTTGCCATTCCAGAAGCCAG (SEQ ID NO:379)
10   PCR product 293 nt

Exon 8
Forward Primer
51524-51546   GATCTGTGTGATGTCGAGGCTTG (SEQ ID NO:380)
15   Reverse Primer
Complement of 51845-51825   GTCCACGTTTCCAGAACACCC (SEQ ID NO:381)
PCR product 322 nt

Exon 9 Fragment 1
20   Forward Primer
52912-52933   CGAAATCCCAAAGACACAGACC (SEQ ID NO:382)
Reverse Primer
Complement of 53722-53701   GAGTTGCTGAAGCTGCGGTAAG (SEQ ID NO:383)
PCR product 811 nt
25
Exon 9 Fragment 2
Forward Primer
53352-53374   GAAAAAGGGAGCTTCTGTGCATC (SEQ ID NO:384)
Reverse Primer
30   Complement of 54172-54153 · .AACAAGGGGACAGGGACTGG (SEQ ID NO:385)
PCR product 821 nt   ·

Exon 9 Fragment 3
Forward Primer
35   53854-53874   CAGAAACCTGGGAGCAGATCC (SEQ ID NO:386)
Reverse Primer
Complement of 54711-54688   GCAACAAGAGGACATGCACCTAAG (SEQ ID NO:387)
PCR product 858 nt

40   Exon 9 Fragment 4
Forward Primer
54266-54288   AAAGGTAGAGGACATGCCAAAGC (SEQ ID NO:388)
Reverse Primer
Complement of 55007-54987 · GGAGCAGCCAACAACTCGTTC (SEQ ID NO:389)
45   PCR product 742 nt ·

These primer pairs were used in PCR reactions containing genomic DNA isolated from

immortalized cell lines for a reference population of 70 human individuals. The PCR reactions were

carried out under the following conditions:

50   Reaction volume   = 20 μl
10 x Advantage 2 Polymerase reaction buffer (Clontech)   = 2 μl
100 ng of human genomic DNA   = 1 μl
10 mM dNTP   = 0.4 μl

Advantage 2 Polymerase enzyme mix (Clontech)   = 0.2 μl
Forward Primer (10 μM)   = 0.4 μl
Reverse Primer (10 μM)   = 0.4 μl
Water   =15.6μl

5

Amplification profile:
94°C - 2 min.   1 cycle

10   94°C - 30 sec.   ⎫
     70°C - 45 sec.   ⎬ 10 cycles
     72°C - 1 min.   ⎭

15   94°C - 30 sec.   ⎫
     64°C - 45 sec.   ⎬ 35 cycles
     72°C - 1 min.   ⎭

Sequencing of PCR Products

The PCR products were purified by Solid Phase Reversible Immobilization using the protocol

20   developed by the Whitehead Genome Center. A detailed protocol can be found at

http://www.genome.wi.mit.edu/sequencing/protocols/pure/SPRI_pcr.html.

Briefly, five μl of carboxyl coated magnetic beads (10 mg/ml) and 60 μl of HYB BUFFER (2.5M

NaCl/20% PEG 8000) were added to each PCR reaction mixture (20 μl). The reaction mixture was

mixed well and incubated at room temperature (RT) for 10 min. The microtitre plate was placed on a

25   magnet for 2 min and the beads washed twice with 150 μl of 70% EtOH. The beads were air dried for 2

min and the DNA was eluted in 25 μl of distilled water and incubated at RT for 5 min. The beads were

magnetically separated and the supernatant removed for testing and sequencing.

The purified PCR products were sequenced in both directions using the primer sets described

previously or those listed, in the 5' to 3' direction, below.

30

Promoter Fragment 1
Forward Primer
30312-30334   GCTCATTTAATCCCCACAACACC (SEQ ID NO:390)
Reverse Primer
35   Complement of 30791-30769   CCACCACACCTGGCTAATTTTTG (SEQ ID NO:391)

Promoter Fragment 2
Forward Primer
30529-30551   TGTAGCTCACCCTCTGGACTTTG (SEQ ID NO:392)
40   Reverse Primer
Complement of 30990-30971   AATATGCAACCCTCCCCTGC (SEQ ID NO:393)

Exon 1
Forward Primer
45   30824-30846   TGAGGCAGAAGAATCGCTTGAAC (SEQ ID NO:394)
Reverse Primer
Complement of 31261-31240   ACTTGTCATTGGCTGTCCCCTC (SEQ ID NO:395)

Exon 2
Forward Primer
32880-32900   TTTGCCTGCACTGTGCTTTTG (SEQ ID NO:396)
5   Reverse Primer
Complement of 33234-33212   CCATACTCAGCATCCTGCACTCC (SEQ ID NO:397)

Exon 5
Forward Primer
10   43330-43349   AACGACAGCAACCAGGGTGG (SEQ ID NO:398)
Reverse Primer
Complement of 43704-43682   CAGCAGGTGTATCTAATGGCAGG (SEQ ID NO:399)

Exon 6
15   Forward Primer
46520-46541   AGAGTGGTGGGGAGATGAGGTG (SEQ ID NO:400)
Reverse Primer
Complement of 46857-46837   TGCAAAGGGGCAGACTAGAGG (SEQ ID NO:401)

20   Exon 7
Forward Primer
49708-49729   CGACCACTTTTATGGGAGGAGC (SEQ ID NO:402)
Reverse Primer
Complement of 49927-49905   CCAGGTGTTCTGAACCACACTTC (SEQ ID NO:403)
25·
Exon 8
Forward Primer
51528-51550   TGTGTGATGTCGAGGCTTGTACC (SEQ ID NO:404)
Reverse Primer
30   Complement of 51779-51758   GAATGCAGGGAAGAGAAGGCAG (SEQ ID NO:405)

Exon 9 Fragment 1
Forward Primer
53017-53038   GCCATCAGGACATGGTGATTTC (SEQ ID NO:406)
35   Reverse Primer
Complement of 53539-53518   TGAGCACTCGTACTTCCCGAAG (SEQ ID NO:407)

Exon 9 Fragment 2
Forward Primer
40   53378-53399   TGAGAGCAGCAGGGATGACTTC (SEQ ID NO:408)
Reverse Primer
Complement of 53948-53926   AAACTCCTGATAGCCACTGGTGG (SEQ ID NO:409)

Exon 9 Fragment 3
45   Forward Primer
53869-53868   AGATCCTCCGCCGAAATGTC (SEQ ID NO:410)
Reverse Primer
Complement of 54583-54560   TTACTCTTCTCTGAGATGCCCGAG (SEQ ID NO:411)

50   Exon 9 Fragment 4
Forward Primer
54334-54355   TGGGCAGTGGCATTGTCTACTC (SEQ ID NO:412)
Reverse Primer
Complement of 54769-54750   TTCCAGGAGGTGGCATTTCC (SEQ ID NO:413)
55

Sequencing reactions were performed using the Big-Dye terminator kit from PE Biosystems (Foster City, CA) according to the manufacturer's instructions. The sequencing products were analyzed on an ABI 477 automated sequencer (PE Biosystems, Foster City, CA).

5   Analysis of Sequences for Polymorphic Sites

Sequences were analyzed for the presence of polymorphisms using the Polyphred program (Nickerson et al., 14 *Nucleic Acids Res.* 2745-2751, 1997). The presence of a polymorphism was confirmed on both the strands. The polymorphisms and their locations in the IL4Rα gene are listed in Table 3 below.

Table 3. Polymorphic Sites Identified in the IL4Rα Gene

Polymorphic Site Number	Nucleotide Position in GenBank Accession	Nucleotide Position in Figure 1	Reference Allele	Variant Allele	Example
PS1	97137(Acc#AC004525)	32884	A	G	1B
PS2	97118(Acc#AC004525)	32903	C	T	1A
PS3	97060(Acc#AC004525)	32961	G	T	1A
PS4	96886(Acc#AC004525)	33135	G	C	1A
PS5[R]	94272(Acc#AC004525)	35749	A	G	1A,1B
PS6	94258(Acc#AC004525)	35763	C	T	1A,1B
PS7	94251(Acc#AC004525)	35770	G	A	1A
PS8	94204(Acc#AC004525)	35817	T	C	1A
PS9	94116(Acc#AC004525)	35905	C	T	1B
PS10	94077(Acc#AC004525)	35944	C	T	1A
PS11	94063(Acc#AC004525)	35958	G	A	1B
PS12	92691(Acc#AC004525)	37330	G	A	1A
PS13	92548(Acc#AC004525)	37473	C	T	1A
PS14	92435(Acc#AC004525)	37586	C	T	1A
PS15	92430(Acc#AC004525)	37591	G	A	1A
PS16	92417(Acc#AC004525)	37604	A	T	1A
PS17	92377(Acc#AC004525)	37644	C	A	1A
PS18	92343(Acc#AC004525)	37678	C	T	1A
PS19	86575(Acc#AC004525)	43446	G	A	1A
PS20	86318(Acc#AC004525)	43703	T	C	1A
PS21	77013(Acc#AC004525)	53008	A	C	1A
PS22	76922(Acc#AC004525)	53099	C	T	1B
PS23	76868(Acc#AC004525)	53153	T	C	1A
PS24[R]	76608(Acc#AC004525)	53413	A	C	1A
PS25	76565(Acc#AC004525)	53456	G	T	1A, 1B
PS26[R]	76516(Acc#AC004525)	53505	T	C	1A, 1B
PS27	76514(Acc#AC004525)	53507	C	T	1A
PS28	76508(Acc#AC004525)	53513	T	C	1A
PS29[R]	76300(Acc#AC004525)	53721	T	C	1A, 1B
PS30	76106(Acc#AC004525)	53915	C	T	1A
PS31[R]	76080(Acc#AC004525)	53941	A	G	1A, 1B
PS32	76072(Acc#AC004525)	53949	G	A	1A
PS33	75784(Acc#AC004525)	54237	C	T	1A
PS34	75553(Acc#AC004525)	54468	T	G	1A, 1B
PS35	75410(Acc#AC004525)	54611	T	C	1A
PS36	75323(Acc#AC004525)	54698	T	C	1A, 1B
PS37	75321(Acc#AC004525)	54700	T	C	1A
PS38	75280(Acc#AC004525)	54741	C	T	1A
PS39	75241(Acc#AC004525)	54780	C	G	1A
PS40	74938(Acc#AC004525)	55083	A	G	1A
PS41	74879(Acc#AC004525)	55142	G	A	1A
PS42[R]	74693(Acc#AC004525)	55328	G	A	1A
PS43[R]	74591(Acc#AC004525)	55430	C	T	1A
PS44	74482(Acc#AC004525)	55539	C	T	1A
PS45	74263(Acc#AC004525)	55758	G	A	1A

[R]Previously reported in the literature

Example 2

This example illustrates analysis of the IL4Rα polymorphisms identified in the Index Repositories for human genotypes and haplotypes for all polymorphic sites except PS1, PS9, PS11, PS21, PS22, and PS23.

5   A sampling of different genotypes containing these polymorphisms that were observed in these reference populations are shown in Table 4 below, with the haplotype pair indicating the combination of haplotypes determined for the individual using the haplotype derivation protocol described below. In Table 4, homozygous positions are indicated by one nucleotide and heterozygous positions are indicated by two nucleotides. Missing nucleotides in any given genotype in Table 4 can typically be inferred based

10   on linkage disequilibrium and/or Mendelian inheritance.

Table 4. Genotypes and HAP Pairs Observed for the IL4Rα Gen

	PS 2	PS 3	PS 4	PS 5	PS 6	PS 7	PS 8	PS 10	PS 12	PS 13	PS 14	PS 15	PS 16	PS 17	PS 18	PS 19	PS 20	PS 24	PS 25	PS 26	PS 27	PS 28	PS 29	PS 30	PS 31	PS 32	PS 33	PS 34	PS 35	PS 36	PS 37	PS 38	PS 39	PS 40	PS 41	PS 42	PS 43	PS 44	PS 45	PS	HAP PAIRS
1	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G	2	2
2	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	T	T	C	G	G	C	T	T	T	T	C	C	G/A	G	A/G	C	C	A/G	2	3
3	C	G	G	G/A	C	G	T	C/T	G	C	C	G	A	C	C/T	G	T	A	G	T	C	T	T	C	A	G	C	T	T	T/C	T	C	C	A	G	G	C	C	G	2	4
4	C/T	G	G	G/A	C	G	T	C	G/A/C	C/T	C	G	A	C	C/T	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G	2	15
5	C	G	G	G/A	C	G	T	C	G	C	C	G	A	C	C/T	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G	2	16
6	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C/T	G	C/T	A	G	T	C	T	T	C	G	G	C	T	T	T/C	T	C	C	A	G	G	C	C	G	2	36
7	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	A/G	C	C	G	2	39
8	C/T	G	G	A	C	G	T	C	G	C	C	G	A	C	C/T	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	A/G	C	C	A/G	2	48
9	C	G	G	G/A	C	G	T	C/T	G	C	C	G	A	C	C	G	G	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A/G	C	C	A/G	3	2
10	C	G	G	A	C	G	T	C	G	C/T	C	G	A	C	C	G	G	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A	3	24
11	C	G	G	G/A	C	G	T	C	G	C	C	G	A	C	C/T	G	C/T	A	G	T/C	C	T	T	C	A	G	C	T	T	T/C	T	C	C	G	G	A	C	C	A	3	44
12	C/T	G	G	G/A	C	G	T	T	G	C/T	C	G	A	C	T	G	C	A/C	G/T	T/C	C	T/C	T/C	C	A	G	C	T/G	T	T	T	C	C	G/A	G	A/G	C	C	G	4	5
13	C	-	-	G	C	G	T	C/T	G	C	C	G	A	C	C	G	C/T	A/C	G/T	T/C	C	T/C	T/C	C	A/G	G	C	T	T	T	T	C	C	G	G	A	C	C	A	4	46
14	-	G	G	G/A	C	G	T	T	G	C	C	G	A	C	C	G	C/T	A/C	G/T	T/C	C	T/C	T/C	C	A/G	G	C	T	T	T	T	C	C	A	G	A	C	C	A	7	2
15	C	G	G	G/A	C	G	T	C/T	G	C	C	G	A	C	C/T	G	C/T	A	G	T	C	T/C	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G	7	7
16	C	G	G	G/A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T/C	C	C	C	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	A	9	10
17	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T/C	C	C	C	C	A	G	C	T	T	T	T	C	C	G	G	G	C	C	G	12	12
18	C/T	G	G/C	G/A	C	G	T	T	G	C	C	G	A	C	C/T	G	C	C	C	T	C	C	C	C	G	G	C	T/G	T/C	T/C	T/C	C	C	G	G	A	T	C	A	13	14
19	C	G	G	G/A	C	G	T	C/T	G	C	C	G	A	C	C/T	G	C/T	A/C	G/T	T	C	T/C	T/C	C	G	G	C	T	T	T	T	C	C	G/A	G	A/G	C/T	C	A/G	13	38
20	C/T	G	G	G/A	C	T	T	C	G/A/C	C	C	G/A	A	C/A	C/T	G	C/T	C	G/T	T	C	T/C	T/C	C	A/G	G/A	C	T	T	T	T/C	C	C	A	G	G	C	C	G	15	51
21	C	G	G	A	C	G	T	C	G	C/T	C	G	A	C	C	G	C/T	C	G/T	T	C	T/C	T	C	A/G	G	C	T/G	T	T	T/C	C	C	A	G	A	C	C	G	17	22
22	C	G	G	G/A	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	C	T	C	G	G	C	C	T	T/C	T	C/T	C	G	G	A	C	C	G	21	10
23	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	A/G	T	C	T/C	C	C	A/G	G/A	C	T/G	T/G	T/C	T/C	C	C	G/A	G	A/G	C	C	A	23	4
24	C/T	G	G	A	C	G	T	C	G	C	C	G/A	A	C	C/T	G	C/T	C	G/T	T	C	T/C	T	C	G	G/A	C	T/G	T	T	T/C	C	C	A	G	A	C/T	C	G	28	31
25	C	G	G	A	C	G	T	C	G	C	C	G/A	A	C	C/T	G	C/T	A	G/T	T/C	C	T/C	T/C	C	A	G/A	C	T/G	T	T/C	T/C	C	C	G	G	A	T	C	A/G	29	37
26	C/T	G	G	G	C	G	T	C/T	G/A/C	C	C	G	A	C	C/T	G	C	A	G	T	C	T/C	C	C	A	G	-	G	T	C	C	C	C	G	G	A/G	C/T	C	A	32	33
27	T	G	G	A	C	G/A	T	T	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	A	G/A	C	T	T	T	C	C	C	G	G	A	C	C	A	41	8
28	C/T	G	G	G	C	G	-	-	G	C/T	C	G	A	-	-	G	C	A	A/G	T	C	T	T	C	A	G	C	G	T	T/C	T/C	C	C	G	G	A	C/T	C	A	41	41
29	C/T	G	G	G	C	G	-	-	G	C/T	C	G	A	-	-	G	C/T	A	G	T	C	T	T	C	A	G	-	G	T	T	C	C	C	G	G	G	C/T	C	A	41	44
30	C	G	G	A	C	G/A	T	T	G	C	C	G	A	C	C/T	G	C/T	A/C	G/T	T	C	T/C	T	C	A/G	G	C	T	T	T	T	C	C	A	G	A	C	C	G	43	22
31	C	G	G	G/A	C	G	T	C/T	G	C	C	G	A	C/A	C/T	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	G	44	3
32	C/T	G	G	G/A	C	G	T	T	G	C	C	G	A	C	T	G	C/T	A	G/T	T	C	T/C	T	C/T	A	G/A	C	T	T	T	T	C	C	G	G	A	C	C	A	44	5
33	C	G	G	-	C	G	T	C/T	G	C	C	G	A	-	-	G	C/T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	A	44	8
34	C	G	G	G/A	C	G	T	T	G	C	C/T	G	A	C	C/T	G	C/T	A/C	G	T	C	T	T	C/T	A	G	C	T/G	T	T/C	T/C	C	C	G	G	A	C	C	A	44	30
35	C/T	G	G	G/A	C	T/C	T/C	C	G	C/T	C	G	A	C	C	C	C	C	T	T	C	C	T/C	C	G	G	C/T	T/G	T	T/C	T	C	C	A	G	A	T	T	A	46	34

The haplotype pairs shown in Table 4 were estimated from the unphased genotypes using an extension of Clark's algorithm (Clark, A.G. (1990) *Mol Bio Evol* 7, 111-122), as described in U.S. Provisional Patent Application filed April 19, 2000 and entitled "A Method and System for Determining

5   Haplotypes from a Collection of Polymorphisms". In this method, haplotypes are assigned directly from individuals who are homozygous at all sites or heterozygous at no more than one of the variable sites. This list of haplotypes is then used to deconvolute the unphased genotypes in the remaining (multiply heterozygous) individuals.

By following this protocol, it was determined that the Index Repositories examined herein and,

10   by extension, the general population contains the 53 human IL4Rα haplotypes shown in Table 5 below.

Table 5A. Haplotypes Observed for the IL4Rα Gene

HAP ID	PS 2	PS 3	PS 4	PS 5	PS 6	PS 7	PS 8	PS 10	PS 12	PS 13	PS 14	PS 15	PS 16	PS 17	PS 18	PS 19	PS 20	PS 24	PS 25	PS 26	PS 27	PS 28	PS 29	PS 30	PS 31	PS 32	PS 33	PS 34	PS 35	PS 36	PS 37	PS 38	PS 39	PS 40	PS 41	PS 42	PS 43	PS 44	PS 45
1	C	G	G	A	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
2	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G
3	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	A
4	C	G	G	A	G	G	T	T	G	C	C	G	A	C	C	G	T	A	G	T	C	T	C	C	G	G	C	T	T	C	T	C	C	A	G	G	C	C	A
5	T	G	G	G	G	G	T	T	G	C	C	G	A	C	T	A	C	C	T	C	C	C	C	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	G
6	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	A	A	G	T	C	T	C	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	A
7	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	C	C	C	G	A	C	G	G	T	T	C	C	G	G	G	C	C	A
8	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	T	C	C	T	C	G	G	C	T	T	T	T	C	C	A	G	A	C	C	A
9	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	T	C	C	C	C	G	G	C	T	T	T	T	C	C	G	G	A	T	C	A
10	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	C	C	C	G	G	C	G	T	C	T	C	C	G	G	A	C	C	A
11	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	T	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
12	C	G	G	G	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	C	C	C	G	G	C	T	C	T	T	C	C	A	G	A	T	C	A
13	C	G	G	G	C	G	T	C	G	C	C	G	A	C	T	G	C	C	T	T	C	T	C	C	A	G	C	G	C	C	C	T	C	A	G	G	C	C	A
14	T	G	C	G	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	G	G	C	T	T	T	T	C	C	A	G	A	C	C	A
15	C	G	G	G	C	G	T	T	G	C	C	G	A	A	C	G	C	A	G	T	C	C	C	C	A	G	C	T	G	T	C	C	C	G	G	A	C	C	G
16	C	G	G	A	C	G	T	C	G	C	C	A	G	C	C	G	C	A	G	C	C	C	T	C	A	G	C	T	T	T	T	C	C	G	G	G	C	C	A
17	C	G	G	G	C	G	T	C	G	C	C	G	A	A	C	G	C	C	G	C	C	C	C	C	A	G	C	T	T	C	T	C	C	G	G	A	A	C	A
18	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	T	C	C	C	C	A	G	C	T	T	T	T	C	C	G	G	A	C	T	A
19	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	C	C	C	G	G	C	T	T	T	T	C	C	G	G	A	C	C	A
20	C	G	G	A	C	G	T	C	G	C	C	G	A	A	C	G	C	A	G	T	C	C	T	C	A	G	C	T	G	C	T	C	C	G	G	A	C	C	A
21	C	G	G	A	G	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
22	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	A	T	T	C	T	C	C	A	G	C	T	T	T	C	C	C	G	G	A	T	C	A
23	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	C	C	C	A	G	C	C	T	T	T	C	C	G	G	A	T	C	A
24	T	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	C	C	A	G	C	T	T	C	C	C	C	G	G	A	C	T	A
25	C	G	G	G	C	G	T	C	G	C	C	G	A	A	C	G	C	A	G	T	C	T	C	C	A	G	C	G	T	T	T	T	C	G	G	A	C	C	A
26	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	T	C	T	C	C	G	G	C	T	T	C	C	C	C	G	G	A	T	C	A
27	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	C	C	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
28	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	T	T	C	G	G	A	C	C	A
29	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	C	G	T	C	C	C	C	G	G	C	T	T	T	T	C	C	G	G	A	C	C	A
30	C	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	C	C	G	G	C	G	T	T	T	C	C	G	G	A	T	C	A
31	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	C	C	C	C	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
32	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	C	C	C	C	C	A	G	C	G	T	T	T	C	C	G	G	A	C	C	A
33	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	C	T	C	C	C	C	T	G	G	C	T	T	T	T	C	C	G	G	A	C	C	G
34	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	T	T	T	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G

Table 5B. Haplotypes Observed for the IL4Rα Gene

HAP ID	PS 2	PS 3	PS 4	PS 5	PS 6	PS 7	PS 8	PS 10	PS 12	PS 13	PS 14	PS 15	PS 16	PS 17	PS 18	PS 19	PS 20	PS 24	PS 25	PS 26	PS 27	PS 28	PS 29	PS 30	PS 31	PS 32	PS 33	PS 34	PS 35	PS 36	PS 37	PS 38	PS 39	PS 40	PS 41	PS 42	PS 43	PS 44	PS 45
35	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	T	T	C	A	G	T	T	T	T	T	C	C	G	G	A	C	C	A
36	C	G	G	A	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	T	T	C	G	G	C	T	T	C	T	C	C	A	G	G	C	C	G
37	C	G	G	A	C	G	T	C	G	C	C	G	A	C	T	G	C	C	T	T	C	C	T	C	G	A	C	G	T	T	T	C	C	C	G	A	C	C	G
38	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	T	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	A	A	T	C	A
39	C	G	G	A	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	A	G	G	C	C	G
40	C	G	G	A	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	C	C	C	A	A	A	C	C	A
41	T	G	G	G	C	G	T	C	G	C	C	G	A	C	C	G	C	A	G	T	C	T	C	C	G	G	C	G	C	C	T	C	C	G	G	A	C	C	A
42	C	G	G	A	C	A	T	C	G	C	C	G	A	C	C	G	T	A	G	T	C	C	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
43	C	G	G	A	C	A	T	C	G	C	C	G	A	C	C	G	C	C	T	C	C	T	T	C	G	G	C	T	T	T	T	C	C	A	G	G	C	C	G
44	C	G	G	G	C	G	T	C	G	C	C	G	A	C	T	G	C	A	G	T	C	T	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	A
45	C	G	G	G	C	G	T	T	G	C	C	G	A	C	C	G	T	A	G	T	C	C	C	C	A	G	C	T	T	T	T	C	C	A	G	A	C	C	G
46	C	G	G	G	C	G	T	T	G	C	C	G	A	C	C	G	C	A	G	T	C	T	T	C	G	G	C	T	T	T	T	C	C	G	G	A	C	C	A
47	C	G	G	G	C	G	T	T	G	T	T	G	A	C	T	G	C	C	T	C	C	C	T	C	A	G	C	T	T	T	T	C	C	G	G	A	C	C	G
48	T	G	G	G	C	G	T	T	G	C	C	G	A	C	C	G	C	A	G	T	C	C	C	C	G	G	C	G	T	C	T	C	C	G	G	A	C	C	A
49	C	G	G	G	C	G	T	T	G	C	C	A	A	C	C	G	C	C	T	T	C	T	T	C	G	G	C	G	T	T	T	C	C	G	G	A	C	C	A
50	C	G	G	A	C	A	T	T	G	C	C	A	A	C	C	G	T	A	G	T	C	C	C	C	A	A	C	T	T	T	T	C	C	A	A	A	T	T	A
51	T	T	G	G	C	G	T	C	G	C	C	G	A	C	T	G	C	C	T	C	C	C	C	C	G	G	C	T	T	T	T	C	C	G	G	G	C	C	G
52	C	G	G	G	C	G	T	T	G	C	C	G	A	C	C	G	C	C	C	T	C	C	C	C	G	G	C	G	T	T	T	C	C	G	G	A	C	C	G
53	T	G	G	G	T	G	C	C	G	C	C	G	A	C	G	G	C	C	T	T	C	C	T	C	G	G	C	T	T	C	T	C	C	G	G	A	T	C	A

In view of the above, it will be seen that the several advantages of the inv ntion are achieved and other advantageous results attained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description and shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

All references cited in this specification, including patents and patent applications, are hereby incorporated in their entirety by reference. The discussion of references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

What is Claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence s lected from the group consisting of:

    (a) a first nucleotide sequence which is a polymorphic variant of a reference sequence for Interleukin
    4 Receptor Alpha(IL4Rα) gene or a fragment thereof, wherein the reference sequence comprises
    SEQ ID NO:1, and the polymorphic variant comprises at least one polymorphism selected from the
5   group consisting of guanine at PS1, thymine at PS2, thymine at PS3, cytosine at PS4, thymine at
    PS6, adenine at PS7, cytosine at PS8, thymine at PS9, thymine at PS10, adenine at PS11, adenine
    at PS12, thymine at PS13, thymine at PS14, adenine at PS15, thymine at PS16, adenine at PS17,
    thymine at PS18, adenine at PS19, cytosine at PS20, cytosine at PS21, thymine at PS22, cytosine at
    PS23, thymine at PS25, thymine at PS27, cytosine at PS28, thymine at PS30, adenine at PS32,
10   thymine at PS33, guanine at PS34, cytosine at PS35, cytosine at PS36, cytosine at PS37, thymine at
    PS38, guanine at PS39, guanine at PS40, adenine at PS41, thymine at PS44, and adenine at PS45;
    and

    (b) a second nucleotide sequence which is complementary to the first nucleotide sequence.

2. The isolated polynucleotide of claim 1 which comprises an IL4Rα isogene.

3. The isolated polynucleotide of claim 1 which is a DNA molecule and comprises both the first and
    second nucleotide sequences and further comprises expression regulatory elements operably linked
    to the first nucleotide sequence.

4. A recombinant organism transformed or transfected with the isolated polynucleotide of claim 1,
    wherein the organism expresses an IL4Rα protein encoded by the first nucleotide sequence.

5. The recombinant organism of claim 4 which is a nonhuman transgenic animal.

6. The isolated polynucleotide of claim 1, wherein the first nucleotide sequence is a polymorphic variant
    of a fragment of the IL4Rα gene, the fragment comprising one or more polymorphisms selected
    from the group consisting of guanine at PS1, thymine at PS2, thymine at PS3, cytosine at PS4,
    thymine at PS6, adenine at PS7, cytosine at PS8, thymine at PS9, thymine at PS10, adenine at PS11,
5   adenine at PS12, thymine at PS13, thymine at PS14, adenine at PS15, thymine at PS16, adenine at
    PS17, thymine at PS18, adenine at PS19, cytosine at PS20, cytosine at PS21, thymine at PS22,
    cytosine at PS23, thymine at PS25, thymine at PS27, cytosine at PS28, thymine at PS30, adenine at
    PS32, thymine at PS33, guanine at PS34, cytosine at PS35, cytosine at PS36, cytosine at PS37,
    thymine at PS38, guanine at PS39, guanine at PS40, adenine at PS41, thymine at PS44, and adenine
10   at PS45.

7. An isolated polynucleotide comprising a nucleotide sequence which is a polymorphic variant of a
    reference sequence for the IL4Rα cDNA or a fragment thereof, wherein the reference sequence
    comprises SEQ ID NO:2 and the polymorphic variant comprises at least one polymorphism selected
    from the group consisting of thymine at a position corresponding to nucleotide 237, adenine at a
5   position corresponding to nucleotide 244, cytosine at a position corresponding to nucleotide 291,
    thymine at a position corresponding to nucleotide 501, adenine at a position corresponding to

nucleotide 554, cytosine at a position corresponding to nucleotide 939, thymine at a position

corresponding to nucleotide 1242, thymine at a position corresponding to nucleotide 1293, cytosine

at a position corresponding to nucleotide 1299, thymine at a position corresponding to nucleotide

10 1701, adenine at a position corresponding to nucleotide 1735, thymine at a position corresponding to

nucleotide 2023, guanine at a position corresponding to nucleotide 2254 and cytosine at a position

corresponding to nucleotide 2397.

8. A recombinant organism transformed or transfected with the isolated polynucleotide of claim 7,

wherein the organism expresses a Interleukin 4 Receptor Alpha(IL4Rα) protein encoded by the

polymorphic variant sequence.

9. The recombinant organism of claim 8 which is a nonhuman transgenic animal.

10. An isolated polypeptide comprising an amino acid sequence which is a polymorphic variant of a

reference sequence for the IL4Rα protein or a fragment thereof, wherein the reference sequence

comprises SEQ ID NO: 3 and the polymorphic variant comprises one or more variant amino acids

selected from the group consisting of threonine at a position corresponding to amino acid 82,

5 histidine at a position corresponding to amino acid 185, isoleucine at a position corresponding to

amino acid 579, serine at a position corresponding to amino acid 675, and alanine at a position

corresponding to amino acid 752.

11. An isolated antibody specific for and immunoreactive with the isolated polypeptide of claim 10.

12. A method for screening for drugs targeting the isolated polypeptide of claim 10 which comprises

contacting the IL4Rα polymorphic variant with a candidate agent and assaying for binding activity.

13. A composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in

the Interleukin 4 Receptor Alpha(IL4Rα) gene at a polymorphic site selected from PS1, PS2, PS3,

PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20,

PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39,

PS40, PS41, PS44, and PS45.

14. The composition of claim 13, wherein the genotyping oligonucleotide is an allele-specific

oligonucleotide that specifically hybridizes to an allele of the IL4Rα gene at a region containing the

polymorphic site.

15. The composition of claim 14, wherein the allele-specific oligonucleotide comprises a nucleotide

sequence selected from the group consisting of of SEQ ID NOS:4-79, the complements of SEQ ID

NOS: 4-79, and SEQ ID NOS:80-231.

16. The composition of claim 13, wherein the genotyping oligonucleotide is a primer-extension

oligonucleotide.

17. A method for genotyping the Interleukin 4 Receptor Alpha(IL4Rα) gene of an individual,

comprising determining for the two copies of the IL4Rα gene present in the individual the identity of

the nucleotide pair at one or more polymorphic sites (PS) selected from PS1, PS2, PS3, PS4, PS6,

PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22,

PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41,

PS44, and PS45.

18. The method of claim 17, wherein the determining step comprises:

    (a) isolating from the individual a nucleic acid mixture comprising both copies of the IL4Rα gene,

        or a fragment thereof, that are present in the individual;

    (b) amplifying from the nucleic acid mixture a target region containing at least one of the

5   polymorphic sites;

    (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;

    (d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized

        genotyping oligonucleotide in the presence of at least two different terminators of the reaction,

        wherein said terminators are complementary to the alternative nucleotides present at the

10   polymorphic site; and

    (e) detecting the presence and identity of the terminator in the extended genotyping

        oligonucleotide.

19. A method for haplotyping the Interleukin 4 Receptor Alpha(IL4Rα) gene of an individual which

comprises determining, for one copy of the IL4Rα gene present in the individual, the identity of the

nucleotide at one or more polymorphic sites (PS) selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8,

PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23,

PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44,

and PS45.

20. The method of claim 19, wherein the determining step comprises

    (a) isolating from the individual a nucleic acid molecule containing only one of the two copies of

        the IL4Rα gene, or a fragment thereof, that is present in the individual;

    (b) amplifying from the nucleic acid molecule a target region containing at least one of the

5   polymorphic sites;

    (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region; .

    (d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized

        genotyping oligonucleotide in the presence of at least two different terminators of the reaction,

        wherein said terminators are complementary to the alternative nucleotides present at the

10   polymorphic site; and

    (e) detecting the presence and identity of the terminator in the extended genotyping

        oligonucleotide.

21. A method for predicting a haplotype pair for the Interleukin 4 Receptor Alpha(IL4Rα) gene of an

individual comprising:

(a) identifying an IL4Rα genotype for the individual at two or more of polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45;

(b) enumerating all possible haplotype pairs which are consistent with the genotype;

(c) accessing data containing the IL4Rα haplotype pairs determined in a reference population; and

(d) assigning a haplotype pair to the individual that is consistent with the data.

22. A method for identifying an association between a trait and at least one genotype or haplotype of the Interleukin 4 Receptor Alphagene which comprises comparing the frequency of the genotype or haplotype in a population exhibiting the trait with the frequency of the genotype or haplotype in a reference population, wherein the genotype or haplotype comprises a nucleotide pair or nucleotide located at one or more polymorphic sites selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45, wherein a higher frequency of the genotype or haplotype in the trait population than in the reference population indicates the trait is associated with the genotype or haplotype.

23 The method of claim 22, wherein the haplotype is selected from haplotype numbers 1-53 shown in Table 5.

24. The method of claim 23, wherein the trait is a clinical response to a drug targeting IL4Rα .

25. A computer system for storing and analyzing polymorphism data for the Interleukin 4 Receptor Alphagene, comprising:

(a) a central processing unit (CPU);

(b) a communication interface;

(c) a display device;

(d) an input device; and

(e) a database containing the polymorphism data;

wherein the polymorphism data comprises the genotypes and haplotype pairs shown in Table 4 and the haplotypes shown in Table 5.

26. A genome anthology for the Interleukin 4 Receptor Alpha(IL4Rα) gene which comprises IL4Rα isogenes defined by haplotypes 1-53 shown in Table 5.

POLYMORPHISMS IN THE IL4Rα GENE

```
TGTGAGCTAC TGTGTCTGGC CTGAATAATA AAATTTAAAA CAATTTTTCA
AAAATTCACC ATGAGGTCTC ACTATATTCC CTAGGCTGGT CTCAAACCCC       30100
TGGACTCCAA GTGATCCACC CCACCTTCCC GAGTAGCTGG GACTAGAGAT
GCACACCATT GCACCCAATA GAGCAATACG TTTCTGTTCT TTGTAAATTA       30200
CCTGCTCTAA GGTATTTTTG TTATAGCAGC CTATATGGAC TAAGCTGACT
TGTAACGTTA CTTGAGACTT TAAAGTGTTC CGGTCACTGT TGGAGGGCTC       30300
TGTCTGTGTT AGCTCATTTA ATCCCCACAA CACCTCAATC AGATGGGGCT
ATTCTTAGTC CCACTTTATA GATAAGGAAA CTGAGGCATG GAAGCACAGC       30400
TTGCTCAAGG TTCACATCTA GTCAGTGACA GAGCAGGTAT TTAAACCTCA
GGAAATAATC AGAGAAACAT GTGTAGAGGG TTGTCCAAGG AAGGCCACAT       30500
CCAGAAGCAT CTCCCAGGAC AGTTGTTGTG TAGCTCACCC TCTGGACTTT
GTGGGTCTGG GTGTTGTTTC ATGATTATAG AGAGAGCTCT GTGAACGTGG       30600
AGGACCTGTT GTCGGCAGAG ACACAAATGG CCAGGGCATG GCTGGGCAGC
CGCAGTGGCT CAGGCCTGTA ATCCCAGCAC TTCGAGAAGA CCAGAGGGGC       30700
AGATCATGAG GTCAGAAGTT CAAGACCAGC CTGGCCAACA TGGTGAAACC
CCGTCTCTAC TAAAAATACA AAAATTAGCC AGGTGTGGTG GTGGGCACCT       30800
GTAATCCCAG CTACTCGGGA GGCTGAGGCA GAAGAATCGC TTGAACCCGG
GAGGTGGAGG TTGCAGTGAG CTGAGATTGC ACCACTGCAC TCCAGCCTTG       30900
                                    G
GAGACAGAGC GAGACTCTGT CTCGGAAAAA CAAACAAACA AGCAAACAAA
CAAACAAATA AATGGCCAGG GCAGGGGAGG GTTGCATATT GAATAAGATG       31000
AGCTCTGCTG GAAGCACAGG TCAGCACTAA CCTGCTTCCT CTCTCTCTGC
AGGTGCCTTG GCATCTCCCA ATGGGGTGGC TTTGCTCTGG GCTCCTGTTC       31100
    [exon 3: 31071..
CCTGTGAGCT GCCTGGTCCT GCTGCAGGTG GCAAGCTCTG GTAAGTCACC
                ..31140]
ACTTCTCAAT CATTCATTTG TTGGCTATTA ATGGCGTGCC AGGGTCCTGC       31200
AGTATGTCAC CTGGCCTTAT GGAGATTACA CTGCAGTGGG AGGGGACAGC
CAATGACAAG TGGCCCTGAT TATCAGTAAA TTCTAAAGAT TGTTAGAAAG       31300
TGATGGGAGC CGGGTGCAGT GGCTCACACC TGTAATCCCA GCACTTCAGG
AGGCCGAGGC AGGAGGATCG CTTGAGCCCA GGAGTTCGAG GTCAGCTTGG       31400
GCAACATAGG GAGACCTTGT CTCTACAAAT AATAAAATAT TAGCCAGGTG
TGGCAGTGCA CGCCTGTAGC CCCAGCTACT CAGGAGGCCG AGGTGGGAGG       31500
ATCCCTTGAA CTCAGGAGGT CAAGGCTGCA GTGAACTGTG ATCGCGCCAC
TCCACTCCAG CCTGCGTGAG AAAGTGAGAC CCTGTCAAAA AAAAAGAGAA       31600
GGTGATGGGG AAAGAACACA GAACAGCATA AGAGGGGGTT GGGGAAGCTG
GGTGGAGTGG GGGGGATTGC AGTTGAAAGT AGGGAAGTCA GGGAAGGCCT       31700
CATTGAGCTG ACTTGGAGGA AGCGGGAACC GTGCAGATGT CTGGGGAAGG
CTCATTCTTG GCAGAGAGGC CCTGCACTGA GCCTGGCGGG AGGGTTGAGC       31800
ACAGGAGGGA ATGTGGTGGA GGAGAGTGAG CAGCAGGAGG GAGCAGTGAA
GGTCAGCAAG GTGACAGAGT GGCTGAATCA AAAAAGACCT TGCAGTGTTT       31900
GAGCAGAGGA TCCATATCAT CCATTATGTT CCAAAGGACT CTTCAGGATG
CCGTGTGGAG AAAGGAAGAG GGTGGAAGCC AGGAGGTCTG GAGGGAGGTC       32000
TGGAGTGGAG GAGATGAGAG GCTCCGGATC CCTCTGGGAG GTAGATTTGA
GGACAGATTG GAATTGAGGT GAAAGACAGA GAAAGAGAAG TGGCCAGGAT       32100
GACTCCAAGA TTTCTGACCT AAACTACTGG GAAGGACGCG GTTGTCATTT
CTGAAATGCA GAAGGATGCC AGAAGAGAAG GTACTTTGGG GAGGGGCGGG       32200
AATCAGGAGT TAGTTTTGGA CATGAGATAA GCTTGGAATA TTTATTTGCT
ATCTAAGACA GCTCCTTAAC ATGGTAAGCC CTTATGCAAG TTGTTGTCAG       32300
CTGAGATGGG CGTGGCACTG AGCATGGGAG CATGGAGGCG CCTGAGTGGT
CTCATGCTCA GGTGGTTTAG CAAACTCAGT GTACATCCTG CCAATTCCAG       32400
TCCTGCCATG GCCACTGACA AGCTAGGAGG GCGCTGAAAG GAGAAGGACC
CCGATGTCTC CTCCAGCCCA TCCATCTCCT CTCTCCCATT GGCCAAACCC       32500
AACCGGAAAC TAAAGGCCAA GGGTACCCGG TGATGAAGAC TGTGGTATCA
GCCTCCTGAG CACAGAGAGG GCAGAAAGGG GTGGAGACAA AGAGGGGCGC       32600
```

FIGURE 1A

```
AGATAGTGGG CAAATGGGGA AGTGGCACTT CCCCTAGCTC GAGGGCAGAG
GCTTGGTGTG ATGGAATGGC ACTCCTTAAA CTGCTACATA TTTTCCCTTT      32700
AATTTGGCCA AGAACAAGTT GTCAAGTTTG TGTGAGATAA AGGTGCACTT
GGTTCGTTCT TGTCTAATGG CCCCCGCACC CATGGGTATT TCTTCAGCTT      32800
CCACAGTCAT CCCGACACTA GCTGGGAAGC TCCAGCAGCC CTGGTCCTGG
CCCCAGCTCT GTGGGCGCTG GCCCTCAACT TTGCCTGCAC TGTGCTTTTG      32900
TGCTATTCCC CTTGGTCCTG TTTGGGTGCA AGTCCCCCTC ACGCATTGAG
     T
TTCCTGGGCC GCTCAGGCTG CTCCTGTGTC TCCCCAGGGA ACATGAAGGT      33000
           T     [exon 4: 32988..
CTTGCAGGAG CCCACCTGCG TCTCCGACTA CATGAGCATC TCTACTTGCG
AGTGGAAGAT GAATGGTCCC ACCAATTGCA GCACCGAGCT CCGCCTGTTG      33100
TACCAGCTGG TTTTTCTGCT CTCCGAGTAA GCCTGCGCTG GAGCTGGAGG
           ..33126]              C
TTTGGGGAGG TTGTGCCCAA AGGGTTTGCC CCAAGAGTGA GCTGGGTCCA      33200
GGTGGTGCGC TGGAGTGCAG GATGCTGAGT ATGGTTTGCT GCTGTTTATA
TGGTGTTAGA GGGGAGGTCC CATCTCCAGG GACATGTTAT GTAAGATACA      33300
GTGGAGCGCA TGGTGGGAGT GTTGGTCCAC GTGGCACATG GATACGGCTG
GAATACTGGA CTAGACCAGC AGTTCTCACA CTTTTTGGTC TCAGGACCCT      33400
TTTTCACACT TAAAAATGAG TGAGGACCCA AAGGGCTTTG GTGTAGGTAA
CACATCATTC TATGTTTACC TAATTAGAAC TTGCAATGAA GAAATGGTGT      33500
AATTTTTAAA AAATTAAAAC AATTAAAAAT TTTTTTTCTT ACTGAAATGG
AGGTCTCACT GTGTTGCCCA GGCTGCTCTC AAACTCCTGG GCTCCAGTGA      33600
TCCTCCTGCC TCCGCCTCCC AAAGTGCTGG GATTACAAGC GTGAGCCGCT
GTATCCGGCC CAAAATGGAG AAATTTTAAG TCCCAACAAC ATGCAAGCCC      33700
GCATTCAACA AATCTTCAGA TCAATTACAT GATCACAGGT CATGTAGCCT
CTAGAAAATT CCACTGTACG CCAGTGAGAG AGAGTGAAAA GGCAAATAAC      33800
GTCCCTGTAT TATGATGAAA AGAGTTTTAC CTGGTGGGCC CAGACCACAC
TTTGAGAACC ACTGGACTAG ACCCTTGATT GAGGAGTACG GTGTTGAGAG      33900
TGGAGTCCTC TGTGATGGTG GATGGACCAG GACACATGGC ATAGGAGTCA
GGTGGTTCCC TGGGCTACTC CATGGTGCAC AGGATGCTTC GTTACACTGG      34000
TGCCCAGGAC ATAATCACGT ACACAAGACA CACAGTTACG GGGCAGACTG
GGGATATACG GCACACCAGC ATGCAGCGTT CACCAGTAAA GGTGGTATTC      34100
CATGATTATT CTAAGGTAGA TGGGCTGTGC TTTGTTTCCA TTGGCTTAGT
CCAGGGATTG GCAAACTATG GCCCGTGAGC CAAATCCGGC CCACTGCTTG      34200
TTTTTGTAAA TAAAGTTTTA TTGGAACACA CTGGCTGCTG TAGTTGTAAC
AGAAACTGCA TGGCCCTCCT TTATGTTTTT TGTTTGTTTG TTTGTTTGTT      34300
TGTTTTCTTT GAGACAGAGT TTCGCTCTTG TTGCCCAGGC TGGAGTGCAG
TGGCACAATC TCGGCTCACT GCAACCTCTG CCTCCCGGGT TCAAGCGATT      34400
CTCCTGTCTC AGCCTCCCGA GTAGTTGGGA TTAATGGTGC CTGCCACCAC
ACCCGGCTAA TTTTTCGTAT TTTTAGTAGA GACCGGTTTT CATCATGTTG      34500
GCCAAGCTGG TCTCGAACTC CTGAACTCAG GTGATCCACC CGCCTCAGCG
TCCCAAAGTG CTGGGATTAC AGGCATGAGC CACTGAGCCC GGCCTCCTCC      34600
TTTATCTTAA TTGAAATAAT TCAGAAATGG AAAGTCAAAT ACTGCATGTT
CTCACTTATA AGTAAGAGTT AAATAATGTG TACACATGGG CATTATTCCA      34700
TGTACCATGG AATAACAGAC ATTGAAGACT TGGGAGGGTG GGAGAGGGGT
GAAGGAAGAG AAGTTACTTA ATGGGCATAG TGTACACCAT TTGGGTGACG      34800
GACCCACCAG AACCCCAGAC TTCACCACTA GGCAGCATAT CCAGTGAGAA
CAGATCTGAG GCTTGCCATC AAAATTGCAC TTGTAAGGCC GGGCACTGTG      34900
GTGGCTCGCG GCTGTAATCC CAGCCCTTTG GGAGGCCGAG GTGGGCAGAT
CACTTGAGGT CAGGAGTTCG AGACCGGCCT GGCCAACATG GTGAAGCTCC      35000
ATCTCTACTA AAAATACAAC AATTAACTGG GTGTAGTGGC GCACACCTGT
AATCCCAGCT ACTAGGGAGG CTGAGGCGGG AGAATTGCTT GAGCCCAGGA      35100
GGTGGAGGTT GCAGTGAGCC GAGATCACAT CACTGTACTC TAGCCTGGGT
GACAGTGAGA CTTTGTCTCA GGAAAAAAAA ACAAAAACAA AAAACAAAAA      35200
ACTCGTACCC CCTAAATTTA TACAAATAAC CAAAAAAAAA AAAAAAAAAG
GAAATTGTGT GGCCTTTGAA GTCCAAAATA TTAACTATCT GGCCTGTTAC      35300
```

FIGURE 1B

```
AGAAAAAGTT TGCAGACCCC TGGCCTAGCC CGTGAGATGT GGGTTGGCTG
TTAAGGTGGA ACATTGGAAT TATCTTACGA TGGCCAAACT GTGCGATGCA          35400
GAGCTTATGT TGTTCTAAAT TAATTAGTGC CACCGGTTCT TCCCTTTCAT
GGGCTTTCAG GAACAAGCTA AGTCCCAGGA CCAGGGCCGG CAGCTAGCA          35500
GGTGTGAGGA GCATCCTTGG TGCATGTGGT AAGAGGCTGT GGCCAGCAAG
AGAGGCAACC CTAGTCGGCT GCCCCAGCAC ACCCTGGCCG CTCCCAAGCC          35600
CCCAGATCTG TCCTCACATC CGTGATCGGG AAGCTGGAAG AGTCTGATGC
GGTTCCTGGA GGCATGTCCC GGACACAGCT GTGGGGCCCA GCCAGCCTAC          35700
AGGTGACCAG CCTAACCCAG CCCCTGTGTC TGCAGAGCCC ACACGTGTAT
                                                    G
     [exon 5: 35736..
CCCTGAGAAC AACGGAGGCG CGGGGTGCGT GTGCCACCTG CTCATGGATG          35800
           T        A
ACGTGGTCAG TGCGGATAAC TATACACTGG ACCTGTGGGC TGGGCAGCAG
              C
CTGCTGTGGA AGGGCTCCTT CAAGCCCAGC GAGCATGGTG AGCAGGGCGG          35900
            ..35887]
AGTGCGGCAG GGGTGGCTGG GTGTGTTCCC ACAGCTGCCT GGGCTGAGGG
    T                                          T
TGGGGTGGGC AGGGGAGGAG GTGGGGTCAT AGCAACAGCA GGAGGAAGCC          36000
    A
GCCTGTATTT TCCCAAATCT GATGGGATTC CTGCCCCTGC CTGGGCCTCA
GTCCTCCCAC CTTTGAAACG GAGCTGGTCG CAGTAGACCA CCAAGCCCCC          36100
TTCAGCCCAG CTGTTTCCAC CCCTGAACTT AAGTGCCCAG GAAGGCGTAT
TGAGATGAGG TGTGCTTGCT GGAAGGCATG CCTGCTGCTG ATTGAAAACC          36200
GAACTGGGAA CATTCCTTCC ATTCTGTGTC CACTGGTCAG CTGCTGCGGC
TTTGGATGGT CTTGACCGTG GAAGGCTGAC CTTCTTCTGG TACCCGGAGT          36300
CCCTGCAGGA ATCCCCCTTG AGCTTGCTGG GCTGTGGTGA CAGGAGTTTA
AAACATGCGT TGTATTCCAG TGATGCATGA TATGACATGC ATCACAGGAA          36400
TAAAAACCTG AGGTCTCATG GATATGATTG CTTCAAAGGA GACCAAGTTT
TAAAACAGAT GAATCAAAAT AAAGAAAAAT ACTCAGTAAA TCATCATAAA          36500
GTACAGAGAT GTGGCCAAAG GTGTGAAGGA TGCAGCTGTA AAAGCTGAAG
TTTGAGGCCG GGTGTGGTGG TTCATGCCTA TAATCCCAGC ACTTTGGGAG          36600
GCCGAGCCCA GCGGATCACC GGAGGTCAGG AGTTCGAGAC CAGCCTGGAC
AACATGGTAA AACCCCGTCT CTACTAAAAA TACAAAAAAT TAGTCTGGCA          36700
TGGTGGCAGG CGCCTGTAAT CCCAGCTACT TGGGAGGCTG AGGTAGGAGA
ATGGCTTGAA CCCAGGAGAA GGAGGTTGCA GTGAGCTTAG ATCATGCTAC          36800
TGCCCTCCAG CCTGGGCGAC AGAGTGAGAT TACGTCTCAA AAAAATAAAA
ATAAATAAAA ATAAAAAGAT TTTTTAAAAG CTGAAGTTT GGGTTACTTT          36900
GGCTCATACA CTTTGCCTTC ACTGTAGAAA GGTGGTTAGT AAAGACCAGG
CGCGGTGGCT CATGCCTGGA ATCCCAGCAC TTTGGGAGCC CAGCGCAGGC          37000
AGATCACTTG AGCCCTGGGC TATTGAGGCT GCAGTGAGCT GGGATTGTGC
CACTGCACTC CAGCCTGGGC AACAGAGTGG GACCCTGTCT CAAAAAAGAA          37100
GAAAAAAAGG GTAATTAATA AACACTAAAG TTCTATGTAG AATTTTAGCA
ACATTATTGT TATTATAATC TTCTTTGCTA TGGCTCTGAA TCTGTGTGGT          37200
GCTCCAGAAG TATGCTATGG AGGTTTTGTC GACCAAAAAT CTGGGTGGTG
GCTGTGGTTT GTAGGCCGGG GCTGGGCTGG GTGATGGGGG AGTCACTGCA          37300
TAGATCCTCA CATAGAGGCC GCTTCTCCCG CAGTGAAACC CAGGGCCCCA
                                 A
     [exon 6: 37334..
GGAAACCTGA CAGTTCACAC CAATGTCTCC GACACTCTGC TGCTGACCTG          37400
GAGCAACCCG TATCCCCCTG ACAATTACCT GTATAATCAT CTCACCTATG
CAGTCAACAT TTGGAGTGAA AACGACCCGG CAGATGTGAG TGGGCATGCT          37500
                T
         ..37485]
TTGACGTTTT TCTGTGACCT CTGGGGAACA GGGTGGGTGA CCAGCAGAGG
```

FIGURE 1C

```
CCCAGTCCCT GGAGCCAGGA GCCTGGGAGG CAAGCCCTGG GGCTGGATAG     37600
                                            T          A
CAAATCCCAG GAGCTAGAGA CCTGGCTTCT CACCTGGCTC TGCCCTAGGC
         T                                             A
AAGTCCCTTT GCTTCCTGGC CCCCCACCCC TCACATCAGA GAAGGGGAGT     37700
                                 T
TATCTCTGCA TGCCGCTCCT CCTCTGTAAA GGTAGGGCTG TGGGCCACAT
CTGTGTTTCC CAGTTTGGGG GACACAAGTG ATCGTAGGTG GCACATTGAC     37800
AGCTCACTTG AATAACCCTA TTATTGAAGA GAATAATACT GACTCAAGAG
ACAGTGACCC GTGTCAGTTC CCTTTTGAGG CCAACGGGTT AAGGAGGAAG     37900
TCCCCATACA GCTGACTCGT TTACTAATTC CTCTTAATGA AGAGAGCAGA
GGCCACACCC CAGGCTTAGA CTTTCCCAAG AAAACAAGAT CAGTTTGTTG     38000
GTTGTTCCCC ATGGAAGCTG GTCCTGACAT TCCCTTCACA GTAGTGTTGG
TGGAGTTTTT GTTGTTGTTT GTTTTGAGAC AGAGTCTCAC TCTGTCACCC     38100
AGGGTGGAAC ACAGTGGCGT GATCTTGGCT CACTGCAACC TCCGCCTCCT
GGGTTCTAGC GATTCTCCTG CCTCAGCCTC CTGAGCAGCC GGGACTACAG     38200
GCACCTGCCA CCGTGCCCAG CTAATTTTTG TATATTTAGT AGAGATGGGG
TTTCACTGCG TTGGCCAGGC TGGTCTCAAA CTCCTGACCT CAGATGATCC     38300
ACTCGCCTTG GCCTCCCAAA GTGCTGGGAT TACAGGTGTG AGCCACCGCA
CCTGGCCAGT GGAGTTCCTT CTTAAGTACA TGTATTGACA TCTTTAAAAA     38400
GGGCGAGAGG ATTTACAGGA AACTATCAGG TCAGTAATGG CAGGGGCCGT
CCACAGTGGG TGGCTGAGTC CCCCTATTTT TCTGCTGGTG TGCAGGGAGG     38500
TCATTTCCTG CCACCCATGT TTCCCCACCC TGAATCCACC TTCCTCACAT
TCCCATTGGA GGGACAATCT CTGGACATAT GGGACCTGGG GTCCCACAGG     38600
GCTGCAATCC AATGCCTGCT GTGCCACTCG CCAGCTGTGT GATGTTGGGC
ATATCCCATA ACCTCTTTGT GCCTCAGTTT CCTCATCTGT AACACAGGAG     38700
TGACAAGAGC ACCCGCCCAC AGGGCTATGA CAGTACAAGG TGTGTGATAC
AGATGAGCTC CCCTGTTTGG CCCACATGTG TCCTAAAAGC CATGTGCCCT     38800
TTCTCTTGAG TGCCCCAGGC CACAGAGATC CCCATCTGCC CGCTGTCCCA
CACACTGGTC TGTCATTTGT TCCTTGAGGT TTGTGAGGGC CGGCTCTGTG     38900
CATCCCAGGG GCCCAGGCTG GGCCTGGTTG GCTCTCAGGG AGCAGGCACC
CGCCACCTTA AGCTCCCATG CTGGTGTCTG TCACTGCTTC CTCTCAATCT     39000
GGCCAAGCCA GGGGTGTCGA TTTATATCTC TCAGGTCTGG TTTCCCCTTT
GGCACTGGGC CAGGTATGGG GAAAGAGCAG GAATGGGGCA GTTGGCTCAC     39100
ACAGCAGAGG CTCAGAAAGC GGGGGGGCATG GGGGGAAGGA GTGCACAGAT
GCTAGAGAGT GGGGCAAGTT TTGTTTGGTC AATAAATCTC CTTCTCATGC     39200
CCCAGGCCTG TGCAAGACCT ACAGAGAGTC CCAAGGATGG GCTGGGGGGA
AGAGAAAGGT ACCACCTTCA GAGTCCAAAG ATATGTTATT TAATATTTTC     39300
ATATTTCTAG ATCTGCCTTC AGGCATGGCT GGATCCAGCT TCTAGGAACC
TGTCCAGCTC TGCGCCCTGC TTTATTCTGT ATTGGCTTCG TTTTTAGGCA     39400
GGCTCTTCCC TCATGTAGTG GCAGATATGC CTACTAGTTG CTCCAGGCCT
ACATCCCAAA GCCACAGTGG GAAAAGGGTT TTTTTTCTTG ACGGTTCTAA     39500
TAAGAGTCCT AAGGCTGCTG CTCAGTGGCC TGGCTTCGAT GCTGTGCCAG
CCTCTGAACC AATCACTGGC TGTGGGTGGA GAGAGGGTGC TGGTGGAGGG     39600
CCCTGCTTGT CCAGGGAGGA GTCACATACC TGCCTCTAGG GCTGCAGGTG
GGCTCAGCTC CATCCAAACC AGATGAACTG AAAATAAGGC AGGAGTGGCT     39700
TCCCCAGGGG AAACTGGGGA AGAGGAAGCA GGACTGTGCT GGCTAAAATG
CCAGCCAGGT TTAAGACGTG GCACCAGATG CCAGTCATGG GATTGGATTG     39800
GTCAGCATGC CTGGGCTATG GCTTAGGGGT ATGTTGGTGC TCAGGGATGC
CACAGGCCTC CAGATACCAG GTCTGAGGCA GAAGAATGAA GTCCAGCTTC     39900
TCTTGTGGGT GGAACAGTGG CAACTGAGAT ACCCCATCTC TCCCTTCCCA
AGAACAGAGC TGAACATAAA GAATTTAGTG ATTGGCCAGA GCTTGGCCAC     40000
ATGCTCCCCT CTGATGAATG ATAGGCCAGG TGATGGGATT GGCACAATTG
GCTTAGACTA ATGAGGGTTG GCCCTGGAGT TGCAGGCAGT GGAGTTCTGT     40100
CCTAAGCAGT GGGCACCTAA ACCCGATGGC ATAAAAGCTG GCGGGGTGTC
CACCTGCATC TGCCACAGCA CTATAGGCAC CAACTGTGGC TCATACTGAG     40200
TGGGATAAAT TCCAGAAAGA AACATTAGGA ACTTACTATA GAATTTTGGG
```

FIGURE 1D

```
GCTAGAGCTA CTCATTCATT CCCCTAGATA ATTTCTAGGC AAGGTTCCAT          40300
AGTGGAGGGG GAGTTTTGGC TTGGGCATTG AAGGATGCAT AGGAGTTTTC
TAGATGGGGA AAGAAGGGAA CGGTAGACCA GGCAGAGGGA ACTGCATGAT          40400
AAAAGGTTTA TGGGTGTGAA AATTCATGGA ATGTTTGAGG ATTATGGGGT
TGGGGGATGT GGGAATATGT GTAGCGATAA AGCACCAAAC AAAGCCAAAA          40500
GTTTAGTTAG AGCCCTGAAT GCCTGCCTCA TAATGGTTTC CATATTTTAT
ATGCCTACTA TGTGCCAGGC ACATTGCTCA GGGTCACACA GCTGGAAATG          40600
GCAGGGCTGA GTTTTTGTTG TTGTTGTTGT TGTTGAGACA GAGTCTCACT
CTATCACCCA GGCTGGAATG CAGGGGCGTG ATCATGGCTC ACTGCATCCT          40700
TGACTTCCTG GGATCAGGTG ATTCTCCCAC CTCTGCCTCC CAGGTAGCTG
GGACTACAGG CACAGGCCAC CACGCCAGGC TAATTTTTTG TATTTTTAGT          40800
AGCGACAGGG TCTCGCCATG TTGTCCGGGC TGGTCTGGAT CTCCTGGCTT
CAAGTGATCC CCCTGGCTCA GCCTCCCAAG GTGCTGGGAT TACAGGCTTG          40900
AGCCACCGCA TCCAGCCCAG ATCTGAGATT TGCACCCAGT ATTTGAACTC
CCAAGCCTGT GCTCTTTTTC CTCCCATGGA CATTTCTCTC AGAGATGGTC          41000
TCCCAAACAC CTGTCCTTCT TGTTAAAAAA CAGACAAACC GCAAGTAGTT
CTTTGGAAGC TCAGATTTCT CTTTTGTTTC TTAGTAAAAC ATTTCCCAGT          41100
TCCCAGCTCC CTTCCAGGGT GTAAGATTTC TTCGGTAACT TACATCTAGC
TGTTGCTTCT TGTTTGCTCA TGTTTAGAAA GAAAGACAAA AGAGAGTGAG          41200
AATTTTCTCT CCCTTCCCCA GTCTCCCCAC AACTCACACC CCACCCTCAG
CTCCCTCTGT AATAGGAAAA TCTCTGAACT CTCTGTAGTT GCTCCAGCAA          41300
TCTTTTGGAA CTTTGCTTCT TTCTTGTGAA AAAACCTCCC CTTGGCTCAC
TTTGCACCAG GTTTCCCCAA ATGTGCTTCC AACCACAAGC AGAAATGGAG          41400
CTGCCAGTAA CCAGGAAGAA ACTGCCGGGG GCTGAGGAAG AGGAGAGGGA
GGTGCATAGC CCTGGATCTC GCAGGGAGAG GGGTGACAGG ATGAGAACTC          41500
AGGTTGCTCA CTTGCCATCA GGGTCAGTCA TGAATATAGC GTTCATGTAT
CACTTTTTAA AGCTTTTTTG GAGGGTAAAA GTAATAGTTA CACAAAATAA          41600
AAATACAAAT GGTACAAAAG GACTTAGAAT GGAAACATGT TTCTCTCCCG
ACTCCAGCCT CCTGTTTTTC TTCCCAGAGA CTGACCACTG CTGTCTGTCT          41700
CTTGCCAGAA GGGAAAGGGA GGCAAGGTTA GGGCAGGCAG AGGGCATGTG
CATCCTTTAG AGAGAGCTTA TGTCTATACA AGCAAATGTG TGTGTTCAGT          41800
CATCGCTGTC TTAGTTTTCT ATTGCTGCAT AATAATGGTA CTACCAGCTT
CACAGCTTTA AACAACACCC ATTTATTATC TCATAGTTTC TGTGGTTGGG          41900
AGTCTGGACA TAGCTTAGCC AGGTTCTCTG CTTTAGAGTC TCGTGAGGCT
ATAATCAAGG TGTGGGATGG GGCTGCAGTT TCATCTGAGG CTCAATTGGG          42000
GAAGGGTCAC TTCTAAGCTC ATACAATATT GGTGACATTC AGTCCCTGGC
AGGCTGTTGA ACTGAGAGCC TCAGTTTCGT GCTGGCTGTT GGTTGTAGTT          42100
AACCCTGAAT TCCTTCCCAT GTGCCCTTTG CAAAGCCATC AAGGCAGAGA
GACTTGCCTA GCAAGTAGGA TATTACAGTC TTCTGTAATA TAATCACATC          42200
CATGAAATCC TCTATATATC CCATCACCTT TACCATATTC TGTGGGTTAG
AAACAAGTAG CAGGTCCTGC CCACACTCGA GAAGACCAGA TGACACAAAG          42300
ATGTGATTCA AAGTGGGGAT CATCGGGGCC ATCTTAGGTT TGTCTGCAGT
GATCACTGTG CCATCTCTCT CTCTCTCTTT TTTTTTTTT TTTTTCCGAG          42400
ACGAAGTCGT CACTCTGTCA CCCAGGCTGG AGTGCAGTGG CATGATCTCA
GCTTACCACA ATCTCTGCCT CCCAGGTTCA AATGATTCTT CTGCCTCAGC          42500
CTCCTGAGTA GCTGGGATTA CAGGTGCCCG CCACCACACC CAGCTAATTT
TTGTATTTTT AGTAGAGACA GAGTTTCACC ATGTTGGCCA GGCTGGTCTT          42600
GAACTCCTCA CCTCAAGTGA TCCACCCACT TCGGCCTCCC AAAGTGCTGG
GATTACAGGC ATGAGCCACC ATGCCCAGCC CCATCTCTCT TTAAAAAACA          42700
AACAAACAAA CAAAAAACAT AAAAAGAAGC AGAGAACACA TACACATCTG
CATCTTCCCT TGTTTACTTA ACAATAGATC TTGGAAGTCA CTTCTCAGTA          42800
GAGGCTAGGT TGGGCAGAGC ATTGGATTCT AGGCCAGTGA GTTTGGACTT
GACCATGGAG ACACTAGGAA GCCCATGAAG GACAGAGAGA GATGCCTCGA          42900
CCCTGCCAGT CCTTTAGAAA GATCACCCAG TGCTTTTTGT ATACCAAACC
CTATTTGAAA TACTTACGTA TATTAACCCA TTTCCTTATC ACCACAACCC          43000
TGCGGGAAGG GAGATAGGCA CTTTTATTAT CTTCATTTTG CAGATGAGGA
CATTGAGGTC CAGAGAGGTT ATGTCACTTA CTTAAGGTCA CACAGCCAGG          43100
```

FIGURE 1E

```
AAGTGGTAGT AGGGACTCTT ACCCTTGTTT TACAGATGAG ATTGAATTAT
CTCACGAAAA CTCAGAAAGG TTAAACAACT- TGCCTAAGTA ACATACAGCT    43200
AATTAGTCGA GGAGCCTGAC 'GCATGTTGCT CTAGCCTGGT CACAGTTACA
GAGGTGGCAA GCAATGGCCT GAACAGGACG AACAACCAAA TACCCAGGCT    43300
GGTGGCTCTT AAACATGGTG GGGTCAGCTA ACGACAGCAA CCAGGGTGGG
CACTGGTGCC CCTCGCCCCC GGCTGGTGCC CTAACATCTC CCTTTTCTCT    43400
ACCAGTTCAG AATCTATAAC GTGACCTACC TAGAACCCTC CCTCCGCATC
                                                      A
       [exon 7: 43406..
GCAGCCAGCA CCCTGAAGTC TGGGATTTCC TACAGGGCAC GGGTGAGGGC    43500
CTGGGCTCAG TGCTATAACA CCACCTGGAG TGAGTGGAGC CCCAGCACCA
AGTGGCACAA CTGTGAGTAT CAAGAGGCCT AAGCAATGGT AATCTCCACT    43600
              ..43562]
CTCCATTCTT CCCCTGTGGC CAGACACTTC CCCTGGCTGA GTCTCTGGGC
TTTTATATCA TAGGATGCCT CTAATGGCAA TCCTGCCATT AGATACACCT    43700
GCTGTGGTGT ATCTGCCAGG TAGGCAGGCT AGGCTGCAGT AACACACAAG
 C
CCCACAATTT CCATGGCTTA ACACTATAGG AATATATTTC TTGCTCATGT    43800
AACAAGCTAA CGTGAATGTT GCTGGTTTGT AGGTGGTTTC CCTCCCTGTA
GAAATCTGGG GAGTGAGGTT CTTTCCATCT TGTGGTGCCA TCATTCTCCA    43900
GGACAAAGAT TCTTACCTAC TTTTGTGTCC TGGTTTCCTT TGGCAGCCTG
GTGAAGCCTA TGGACCTCAT TTCAGAATAT TTTTAAATAC ATAAAATCCC    44000
AGCCTGGGCA ATATAGTGAA ACCCCCATCT GTACAAAAAT TAGCCAGGCA
TGGTGGCATG CACCTGTAGT CCCAGGTACT GGGAAGGCTG AGGTGGGAGG    44100
ATCACTTGAG CCCAGGAGTT TGAGGCTGCA GTGAGCCGTG ATCGTACCAC
TTTACTCCCA CCTGGGTGAC AGAGCAAGAG CCCATCTCTA AAAATAAATA    44200
AATACAATGA AATAAAATAA AATAAATAGA ACTACAGAGG AAACTAATTG
TATTGAAATG CAGTTATAAA ACATTTAAAC ACATTTTTAA TCTAGAGATA    44300
TATGTGCTTC TTTATTAAGA TCTATAAATA.ATAAGTTCTA GGGGTAGCTC
GCATAAATAC TGTAATTTCA AAGTAGATAA GCATAAATAA TACTTTATGA    44400
TACTGAAATT GTGATGTGAT ATGAGAATAG CTGTGAGTTT TGTTTTGCTG
GGGACAGGAT CACTGATGCT GTCATTACTG GGGTCTCTTC CCTCCATTCT    44500
TTTTTTAAAA TTGTATTTTA TTTTATTTTT.AAAATTTTAA AATAAATAGA
GACAGGGTAT CACTATGTTG CCCAGGCTGC TTTTGACCTC.CTGGGCTCCA    44600
GTGATCTTCC CATCTTGGCT TCCCAAAGTG CTGGGATTAC AAGTGGGAGC .
CAGTGTTCCT GGCCCCTTCC TCCATTCTTA ATGGAAGGAG ATGCTAGGTG    44700
TGAGAGGTTA GGGAAAGTAA AGATGTAATT TCTTTCCCAT CCAAGTTCTC
AGACCCCTGA ATTCTACCTG CAGCCATGTT GGTCCATCAA CCCCAAGTGA    44800
AGAATCCCTG CTCTAGGGCC CCACCATTGT CTGTATCCAG CCAGCAGAAG
AGGCGTGATT ATGGAGATCA CATCTGCTTC TTGAAAGCAG ACAGCCCGGA    44900
AGTGGGCCGC ATCACTTCCT CTCAAATTCT ATTGGTGAAA ATGGTCACAT
GACTACACAT AGCCACAAAG GAGGCTGGGA ACTTTCTCAC TTGGAACCTA    45000
CATCCCAGAA ACAACTCTTT TCAGTGAGGT ATCCCACAGG TCTTTCGCAG
TAGAAATATT GATTATCTCA CATAAAATGA AGTCTTACAA ATGGACCTAC    45100
TGGGTTTTGT ACAGCAGCCA AGTGATATCT CTTCCCTTCT GCTGTCTTCC
CTTCTGCCGT CCTTCACATG GTGGCATTGT ATCCTTAGAC TTGCCACCCA    45200
TGCCCTCAGG TTGGCCGTTG CACACTGTCT TACATAAAGC AGGAAGGAAA
GGAAAGGCTG CTACGAGAGA GTGTACCTTG TGCATCTCTT TTTTAATCAG    45300
GAAGCAAACA TCTTTCTAGA AGCTTCCCTA GCAAAATTCC CCTTACATCT
CATTGGCCAA GACTGTTACA TGTTACATGG TTACTGTTAT .TACTTGCTCA    45400
TTGCAAGGAA GACTGGGAAC TCAAATGCCT GGAAAAAGGA ACAGGATAAT
CGTGATTGGC TCAAGCCTTA GGGTGGGCAT GGCTCCCTGA CAAGGGAGAG    45500
AGGAAAAAGC TGTTGAGTGA AGAAGACTGC TTCAGTTTCC CCATCTGTAT
AATGGGAGGA GTAAGGGCTG TCGTGAAAAC TCAATGAAAG AAGATTCTTC    45600
AACGTGGTAG GTGCAGTGGC AGCTGGCAGT ACCCTGACCC TGCCACCGCA
CAGCCCTCTC AGCATTGCTC ATCCTGCACT GTGGATATCA GTTGAGCCAC    45700
GTGTCTCCTG CCCTGGGCTG TGAGCTCCAT AGGCAGGGTC TCCATGGCTG
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<div align="center">FIGURE 1F</div>

```
TATCTCCAGA ACCCAGCACA GAACCAGGTG CTTGGGAAAG TTTTGAATTG        45800
ATTCTCATCT GCCATTGGCA TGGGGAAGGG AACTAGCTTG TATGAAACAG
ATAACAATGT ATGGGACCCT CATTCATTAT TTCAGCAAAT ATTTGCTGAG        45900
TTCCTCCTAC ATGGCTAGCC CTGTGCTAGA CACTGGGGAA TCGGCGATGA
ACAAAGCAGA TAGAAATCCC CACTCTTGTG GAGCTGACAT TCTGGAGGGA        46000
GAGACAAAAA GCAAACATAT AAAGAAAGAA AGAAATCACA TGGATCTGGA
TGACAGTGAG TGCTGGGAAG AAAATAAAAG CAGAGGAAGG GGATGGAGCG        46100
ATGGGCAGGG GGCAACGGTA GGGAGGGTGT CGGGGAAAAC TTTTTGGAGA
ATGTGACGAT GAAAGTGAAC AAGGAGAAGT CAACCGTGTT GAGATGATGG        46200
CAGCTAATGA TGTGGACAGG CCACTCTGTT CTGAGTGCAT TATCTATTGA
TTCATCATGT CATCCTCGCA ACAGCCCTGC ACGATCAATT CTGTCATTAA        46300
CCCCATAGTA CAGATGAGGA TGCGGAGGCA CAGAGAAGAT AAGGGACTTG
TCCTGTGTCA CACAGCAAGG AGCCATCCGG CTCCTAAGTT GGTGCATTTG        46400
ACTTCTGTGC TTCCGGAAAG AAAGAGCAGC AAGTTTAAGA TCTGGAGGTG
GCACTGAGCT TTGGAGGAGC AGGGGGCAAT GAGGTGGCCG GTGTGACGAG        46500
GACTCAATGT GCAAGAGGGA GAGTGGTGGG GAGATGAGGT GGAGGGGTGG
TCGGCGGTCA GATCGTGGAG GGTCTCGGAC GAGGGTCCTG ACCCTGGGTC        46600
TCCAGTCCTG GGAAGTGGAG CCCAGGCTGT ACCATGGCTG ACCTCAGCTC
ATGGCTTCCC CTCCCACTTC CAGCCTACAG GGAGCCCTTC GAGCAGCACC        46700
        [exon 8: 46674..
TCCTGCTGGG CGTCAGCGTT TCCTGCATTG TCATCCTGGC CGTCTGCCTG
TTGTGCTATG TCAGCATCAC CAAGTGAGTC CTGGGCCCAG TGCTGCCGAG        46800
                ..46773]
CAGTCCCTCT GGAGTGCAGG GTGGCAGGGA CTTGCCCCTC TAGTCTGCCC
CTTTGCAGTC CTCTCAGTCA ATAATACGTA TTTACTGAGC AGCTACTACA        46900
CACCTTGAGA GTAGAGCTGA GAACATATCG ACAAGGACCC CACTTTTTTC
TTTTTTTCTT TTTTTTTTTT TTTTGAGACG GAGTCTCACT CTGTCACCCA        47000
GGCTGGAGTA TAGTGGCACA ATCTTGCCTA ACAGTAACCT CCGCCTCCCG
GGTTCAAGCA ATTCTTCTGC CTCAGCCTCC AGAGTAGCTG GGATTACAGG        47100
CGCATGCCAC TATGCCCGGC TAATTTTTTG TATTTTTGGT AGAGATGGGG
TTTCACCATG TTGGTCAGGC TGGTCTCGAA CTCCTGACCT CATGATCTGC        47200
CTGCCTCAGC CTCCCAAAGT GCTGGGATTA CAGGTGTGAG CCACTGCACC
CAACCAGGAC TCCACATTTC TAAAACCGGC ATCCTACTGG GGAGACTGAA      47300
AATACATATC AATCACAAAC AGGTGGTTTT CCATAGTGAC CCACTCTCTG
AATGCACTAG ACCAGGGTGG AGGCCAGAGA TCTTCTGGGG TGCTTTTTGC        47400
AAGGGGGACC AGGATAAGGC TCTCCAAGGA GGGAAAATTT GAGGGGGGCC
CTGACTGGGG AGAATGAGCT GGCCAGGGAT AAGCAAGATG GAGTCATCCC        47500
ACATCCCCTT ACAACACTGG GTGCCTGGGC AACTGGGGGC ATTTGGGGGC
ATGTGGTAGG AGCCAGAGGA ATTTGCGACG ATTGCCCTGA TGGAGTCAGG        47600
AGACCTGGGT TTGAATCCTG GCCTTGGAGC TTGGTAGCTG GCGGCCGACA
AGTTGCTGAA ACCCCTGAGC CTGGGGTTCC TGCTTTGCAG AGTGACAGTG        47700
ATGGTGAGAA CATATTTCAT CAGCCAGAAG AGGCCAAATC ACAGTAAAGG
CTGAGGGAGG AGATGAGTGG CGAGTGGCTG GGAGGTGGTG GAAGGAGCCT        47800
CGTTTCCAGA GAGCTCTTGC CAGCCCTTGG AATCATGGTG TCTCAGAGCC
TCAGTCCTCC CATCTCTGAA ATGGGACTAG CAAGCTCAAC CTCACTAAGT        47900
CAGGATTAGA GGTGGCTAAG GATTATTAAC ATGATTGATG AAAGTGCCCA
CTCTTGGCCC AGCACACACT AGGTAGGCAG GGAATGCAAA TTCCCCTCCA        48000
TATCTTGTCA CTGATGCCTC CGAGCAACCT TGGACTGATC GCCTTGCTCT
GAGCCTCAGT TTCCCCATCA CCTGTACCTC TTCCCACTCC CCATCACTAT        48100
ATCCCAGCAT GCCAGCCTCT TTGCTGTTCT TTGTCTTTGG TTTCTTGTTT
TGTTCTGTTT TTTAGACAGG GTCTCACTCT GTTAGCCAGG CTGAAGTGCA        48200
GTGGCGCGGT TACGGCTCAC TGCAGCCTCC AATTCCTGGG CTAAAGAGAT
CCTCCCATTT CAACTTCCAG AGCAGCTGGG ACAACAGGCG CTTGCCACCA        48300
CACCTGGCTA ATTTTCTTAT TTTAATTTAA TTTTATTTTA TTTTTTGGGA
CAGAGTGGAG TCTCAAAAAC CAAGCTAGAG TGCAGTGGTG CGATCTCGAC        48400
TCACTGCAAT CTCTGCCTCC CGGGTTCAAG CGATTCTCCT GCCTTAGCCT
CCCGACTAGC TGGGATTACA GGCGTGTGCC ACGACACCCA GCTAATTTTT        48500
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FIGURE 1G

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GTATTTTTAG TAGAGATGGG GTTTCACCAT GTTGGCCAGG ATGGTCTTGA
ACTCCTGACC TCAAGTGATC CACCCACCTC GTTCTCCCAA GGTGCTGGGT          48600
ACAGGCATGA GCCACTGTGC CTGGCCAATT TTCTTACATT TTGTAGAGAC
TGGCTGTCAC TTATGTAGCC CAGGCTGATC TTGAACTTCT ACCCCTTTAT          48700
CTTTATTCAT GGCACTTATT ACCATGAATG AATGACCTCA TATAAGCATT
TCTTTCGTTT TTTTTTTTTT TTCTTTGAGA TGGAGTCTCA TGTTGTCCCC          48800
CAGGCTGGAG TGCAGTGGCG CGATCTCAGC TCACTGCAAC CTCCGCCTTC
CGGGTTCAAG CGATTCTCCT GCCTCAGCCT CCTGAGTAGC TGGGATTGCA          48900
GGCGCCTGCC ACCATGCCTG GCTAAGTTTT GCATTTTTAG TAGAGACGGT
GTTTCACCAT ATTGGCCAGG CTGGTCTCGA ACTTCTGACC TCAGGTGATA          49000
CACCTGCCTT GGCCTCCCAA AGTGCTGGGA TTACAGGCGT GAGCCGCCAT
GCCTGGCCTC ATATAAGCAT TTCTGTCTCC ATTTATCATC CATCTTTCCC          49100
TCTTGAAGGT CAGTTTCACC AAGGCAGGCA TCTTTGTCTC GTTCACTGTT
GTAGCCTCAG GGCCAGGCAC AGTGAGTCAA ACATAGAAGG TGCTCAATAA          49200
ATATGTGTTT ATTTATTGAA ACCATGGGCA GAGGCTAATT CAGAAGCGGT
CTGAGGACCT TACCTCCCAG TGATGATGCA CCATGGCCCC AGGCAGGCCA          49300
GGAAGAGAGA AGGGTTGTGT TTCTCCGTAG GTCCCCCAGC TTCCCAGGCC
ATCCCAGGCC ATTCCCTGGT CATTTGCCCT CAGCTGCTCT GAAAAAGGGA          49400
TTGTTGAGGG GAACCTAGAA TCCTCTCTCT GCAGTTTGAG TCTTTCCTAA
TCCCCTGGGG TCTCATTCCC ACTGAGGACA TAGGTGGCCT CCTCAGGAAC          49500
TCTGTGCTGG GTAACAGAAT GCGGGAGTGT GAACCTGGCT CTGCCACCTA
CCAGCTGTCA CTCCACCTCC TTGGGCCTCA CTCTCCTCAT CTGTAGAATA          49600
GGGTTAGCAA TAGAATCCAT GTCACCAGGT TAGAATGATG AGTCAGTGGT
TTGACCTCCA GAAACTAATC AGCCTGATCT CTGATGCCAA ATAAGTATTG          49700
GTGATAACGA CCACTTTTAT GGGAGGAGCG TTCACCTGTC AATAATTCAG
AGATCAACAC CTTTTCCTTT TGTTTTTCAG GATTAAGAAA GAATGGTGGG          49800
           [exon 9: 49781..
ATCAGATTCC CAACCCAGCC CGCAGCCGCC TCGTGGCTAT AATAATCCAG
GATGCTCAGG TAGGAGTAGG CGTGGATGAG GACATGTGGG ACTGTGTACA          49900
           ..49859]
TGAAGAAGTG TGGTTCAGAA CACCTGGGCT GTTAAGGACC TTCACTGGCT
TCTGGAATGG CAAATAGACA GTCAGGAGGG TTGCAGGGGA GACAGAGGCA          50000
GAAGCCGAAT GAGGTCATTA GCAGACCAGA GGCTTTCCCG CCCTTCCCCT
TGGCAATCCC AGCCTGGGGT GGGCTTCTCT GGGGTTGGTT TCCTGTTTTT          50100
TTCCCTCCCC TTGGGAGAAT GACCCTTGGG TCATCATCAC TGTGTCATTC
CCTGGGGAGG TGCCAGTACC AGGGCTAGAG GCCAGAAGGA GTGGAGGAAG          50200
GAGAGGGTGA CAGGCTTTCT GTGTCTTCTT CTTAAGCATA GGAAACTGCC
CCCGAAGCAC TAGCAAATCC CTTCCGGGTT CTCATTGGCC TGAAATGTAT          50300
CCCACCCCTA AGCCAGGGGT GGAGTCAGCT TCCCCAAGGC GATGGTCCTG
TGGGTGAGTG GGTGGGGTTT GCCTGAGCAA GATGAGAGTT CTCTAGGTAG          50400
GAGAAAGGGG GATTATAGGT CCTGTCTAGA AGAGAAGGTC TGAGGGTCCT
TGCTTTTCCA GGGACTCTGG AATCTAGTGT TGGCTTTGAA TCCTGACTCT          50500
GCCACTCACT GGCAGTGTGG ACTTGAGCAA GTTGCTTAAT TCTCTGAGCC
TCAGTTTCCT CTTGTGGGTT ATAACAGTGT TTACCTGGTA GGACAGATAT          50600
TGGAATTTAT TGAGACAATA CATATAAAGT GCATATTCCA GCCTCTTGCA
AATACCAAGT GCCATTTATG TATCAGTTAG TGTTTGCTGT GTAACAAATG          50700
ACCCCGAAAT GTAGAGGGTT ACAACAACTT TATTTAGCTT ATGCTTCTGC
AGGCTGGCAT TTGGGGCTGG GCTCAGCAGT GAGGGTGGCG GGGGAGGCTG          50800
GGCTGGGCTG GGCTGGGCAG ATCTGAATTG AGCTGACCCG TCCCCGTAGC
CTCCCTCCGT GTCTGACAGT TGGCTTTTTT TTTTTTTTTC TTTTTCTGAG          50900
ACGGAGTTTT GCTCTTATTG CCCAGGAGTG CAATGGCATG ATCTTGGCTC
ACTGCAACCT CTGCCTCCTG GGTTCAAGCA ATTTTCTTGC CTCAGCCTCC          51000
CAAGTAGCTG GGATTACAGG CATGTGCCAC CACGCCAGGC TAATTTTGTA
TTTTTAATAG AGATGGGGTT TCTTCATGTT GGTCAGGCTG GTCTGGAACT          51100
CCTAATATCA GATGATCCAC CCACCTCAGC CTCCCAAAGT GCTGGGATTA
CAGGCGTGAG CCACTGCACC CAGCCTAGTT GGCTGACTTT TACCTGGGAC          51200
AGTGCAGGTG CCTGAGCCAT GTGCCTCTCA CTCTCCAGCA GGCCGGCCCA
```

FIGURE 1H

```
GGCTTGTTTA CAGAGTGGCT CAGTTTTCAA GGGTGGGAAG TCCCAAGGCT        51300
TCTTGAGGCC TAGGCGCAGC ACTGGCATGA TATCACTTCC ATCACATTCT
ATGGGCCCAA GCAAGTCCCA GGGCCAGTGT AGATTCAAGG GATGGGAGGA        51400
GATTCAGAGC ACTCCTCTGT GGCCACTTTT GCCATCGACC ACAGTCCCTG
TAAATATTAG GACAATGTAA TTAATTCCCA GGAATCTGAG GCTCAGAAAG        51500
CGTAAGTGAC CTGTTGGACT TCTGATCTGT GTGATGTCGA GGCTTGTACC
CCTTCCTGAG CATTGCCGTA CTCCAGGCCG GGCTGCAAGG CCACTCTGCT        51600
CTTTCATTGG CTGTCTCTGT ATTTTAGGGG TCACAGTGGG AGAAGCGGTC
        [exon 10: 51628..
CCGAGGCCAG GAACCAGCCA AGTGCCCGTA TGTATCTGAA CTTAGGTCAC        51700
                ..51677]
AGCCTGCATG CATTGGGAAG GTGATAGAAT TGGAGAGGCA AGCCCCTAGC
TCCATGTCTG CCTTCTCTTC CCTGCATTCG GTAATTGCCC TGTGACATTA        51800
GCCTTCAAGG GACGGCAGGA GGAGGGGTGT TCTGGAAACG TGGACTGCTG
GCCAAGCCCC CTGAGTTTCA CTGGTGTGTC AGGTACATGG TGATACCCCT        51900
TGGGAGTGCT GTTATAGTTA ACAACCAGAG CAGCCGTGCC TGTTGTTAAA
ATCTTGACCT AATTGTATAC TTGTCGGCAA ATAGCCACTA TCCTGAACAC        52000
TCCCCTCCTT TTTTTTAATA TACAGGATCT CACTCTGTGG CCCAGGCTGG
TGTGCAGTGG TGCGATCATA GCTCACTGCA CCTTCAAACT CCTGAGCTCA        52100
AGTGATCCTC CCATCTTAGC CTCCCGAGTA GCTGATACTA CAGATGTGCA
TTACCACGCC TGGCTATTTT AAAAGGTTTT TGCCTGTAAT TCCAGCTACT        52200
CAGGAGGCTG AGGCATGAGA ATCACTTGAA CCCGGGAGGC AGAGGTTGCA
GTGAGCGCAG ATTGTGCCAC TGCACTCCAG CCTGGGCGAC AGAGTGAGAC        52300
TCTTGTCTCA AAAAAAATAA TACCAAAAAA AGTTTTTGTA AAGACAAGCT
CTCGCTGTGT TGCCCCGCCA CTGTGGCCTC CTTAGCTTCT TCCCTGGGGC        52400
CTGCTGGACC TTTCCATACT CCAGAAACTA AAGGGGGTCC AGGACCCTGC
TTCAACCCTA GGATCCCGCA TCTTTTTTTT TTTTTTTTTT TTTTGGACGC        52500
AGGGTCTTGC TGTGTCCCTC AGGCTGGAGT GCAGTGATTC ACTGCAGCCT
CAAACTCGTG GGCTCAAGTG ATTCTCTAGC CTCAGCCTTC TAAGTAGCTG        52600
GGACTACAGT CATACACCAA CATGCCCAGC TAATTTTCCT TTTTTTTAAT
TCTTGTAGAG ATGTTTGAGA CGGCTTGGGC TCTGTTGCCC AGGCTGTTCT        52700
CAAACTCCTG AGCTCAAGCG ATCCTCCCTC CTCAGCCTCC TAAAGTGCTG
GGATTACAGG CGTGAGCCAC CGCACCCGGC TTCCATATCC TTTCTAATTG        52800
GTCATGGCTT GGGATAATGG TGTTGCTTTT AATTATCATC ATCCATAAAG
ACTTTTTCTT ACTCAACAGA TCTGAGCTTG TATTTGGTGC CCAGGACATG        52900
TGCTGGGTTC CCGAAATCCC AAAGACACAG ACCCTACCCT CAGGGATTTC
TCATTCTAGC AACATAGACT GATCAATTAC TGATTATAAC GTTAGAAGGC        53000
ATGTCTGAAG TAGACAGCCA TCAGGACATG GTGATTTCAG GCTGGGCTTT
        C
GAAGAATGAA TAGGAGTTTT TCAAGTGTCG AAACTGAACC CTGACCAACC        53100
                                                    T
TTTGCTTTTG CAGACACTGG AAGAATTGTC TTACCAAGCT CTTGCCCTGT
        [exon 11: 53114..

TTTCTGGAGC ACAACATGAA AAGGGATGAA GATCCTCACA AGGCTGCCAA        53200
        C
AGAGATGCCT TTCCAGGGCT CTGGAAAATC AGCATGGTGC CCAGTGGAGA
TCAGCAAGAC AGTCCTCTGG CCAGAGAGCA TCAGCGTGGT GCGATGTGTG        53300
GAGTTGTTTG AGGCCCCGGT GGAGTGTGAG GAGGAGGAGG AGGTAGAGGA
AGAAAAAGGG AGCTTCTGTG CATCGCCTGA GAGCAGCAGG GATGACTTCC        53400
AGGAGGGAAG GGAGGGCATT GTGGCCCGGC TAACAGAGAG CCTGTTCCTG
        C
GACCTGCTCG GAGAGGAGAA TGGGGGCTTT TGCCAGCAGG ACATGGGGGA        53500
        T
GTCATGCCTT CTTCCACCTT CGGGAAGTAC GAGTGCTCAC ATGCCCTGGG
        C T           C
ATGAGTTCCC AAGTGCAGGG CCCAAGGAGG CACCTCCCTG GGGCAAGGAG        53600
```

FIGURE 1I

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CAGCCTCTCC ACCTGGAGCC AAGTCCTCCT GCCAGCCCGA CCCAGAGTCC
AGACAACCTG ACTTGCACAG AGACGCCCCT CGTCATCGCA GGCAACCCTG     53700
CTTACCGCAG CTTCAGCAAC TCCCTGAGCC AGTCACCGTG TCCCAGAGAG
                C
CTGGGTCCAG ACCCACTGCT GGCCAGACAC CTGGAGGAAG TAGAACCCGA     53800
GATGCCCTGT GTCCCCCAGC TCTCTGAGCC AACCACTGTG CCCCAACCTG
AGCCAGAAAC CTGGGAGCAG ATCCTCCGCC GAAATGTCCT CCAGCATGGG     53900
GCAGCTGCAG CCCCCGTCTC GGCCCCCACC AGTGGCTATC AGGAGTTTGT
                T                                  G        A
ACATGCGGTG GAGCAGGGTG GCACCCAGGC CAGTGCGGTG GTGGGCTTGG     54000
GTCCCCCAGG AGAGGCTGGT TACAAGGCCT TCTCAAGCCT GCTTGCCAGC
AGTGCTGTGT CCCCAGAGAA ATGTGGGTTT GGGGCTAGCA GTGGGGAAGA     54100
GGGGTATAAG CCTTTCCAAG ACCTCATTCC TGGCTGCCCT GGGGACCCTG
CCCCAGTCCC TGTCCCCTTG TTCACCTTTG GACTGGACAG GGAGCCACCT     54200
CGCAGTCCGC AGAGCTCACA TCTCCCAAGC AGCTCCCCAG AGCACCTGGG
                                         T
TCTGGAGCCG GGGGAAAAGG TAGAGGACAT GCCAAAGCCC CCACTTCCCC     54300
AGGAGCAGGC CACAGACCCC CTTGTGGACA GCCTGGGCAG TGGCATTGTC
TACTCAGCCC TTACCTGCCA CCTGTGCGGC CACCTGAAAC AGTGTCATGG     54400
CCAGGAGGAT GGTGGCCAGA CCCCTGTCAT GGCCAGTCCT TGCTGTGGCT
GCTGCTGTGG AGACAGGTCC TCGCCCCCTA CAACCCCCCT GAGGGCCCCA     54500
                G
GACCCCTCTC CAGGTGGGGT TCCACTGGAG GCCAGTCTGT GTCCGGCCTC
CCTGGCACCC TCGGGCATCT CAGAGAAGAG TAAATCCTCA TCATCCTTCC     54600
ATCCTGCCCC TGGCAATGCT CAGAGCTCAA GCCAGACCCC CAAAATCGTG
           C
AACTTTGTCT CCGTGGGACC CACATACATG AGGGTCTCTT AGGTGCATGT     54700
                                                 C C
        ..54692
CCTCTTGTTG CTGAGTCTGC AGATGAGGAC TAGGGCTTAT CCATGCCTGG
                                         T
GAAATGCCAC CTCCTGGAAG GCAGCCAGGC TGGCAGATTT CCAAAAGACT     54800
                                G
TGAAGAACCA TGGTATGAAG GTGATTGGCC CCACTGACGT TGGCCTAACA
CTGGGCTGCA GAGACTGGAC CCCGCCCAGC ATTGGGCTGG GCTCGCCACA     54900
TCCCATGAGA GTAGAGGGCA CTGGGTCGCC GTGCCCCACG GCAGGCCCCT
GCAGGAAAAC TGAGGCCCTT GGGCACCTCG ACTTGTGAAC GAGTTGTTGG     55000
CTGCTCCCTC CACAGCTTCT GCAGCAGACT GTCCCTGTTG TAACTGCCCA
AGGCATGTTT TGCCCACCAG ATCATGGCCC ACATGGAGGC CCACCTGCCT     55100
                                         G
CTGTCTCACT GAACTAGAAG CCGAGCCTAG AAACTAACAC AGCCATCAAG
                                                 A
GGAATGACTT GGGCGGCCTT GGGAAATCGA TGAGAAATTG AACTTCAGGG     55200
AGGGTGGTCA TTGCCTAGAG GTGCTCATTC ATTTAACAGA GCTTCCTTAG
GTTGATGCTG GAGGCAGAAT CCCGGCTGTC AAGGGGTGTT CAGTTAAGGG     55300
GAGCAACAGA GGACATGAAA AATTGCTGTG ACTAAAGCAG GGACAATTTG
           A
CTGCCAAACA CCCATGCCCA GCTGTATGGC TGGGGGCTCC TCGTATGCAT     55400
GGAACCCCCA GAATAAATAT GCTCAGCCAC CCTGTGGGCC GGGCAATCCA
                T
GACAGCAGGC ATAAGGCACC AGTTACCCTG CATGTTGGCC CAGACCTCAG     55500
GTGCTAGGGA AGGCGGGAAC CTTGGGTTGA GTAATGCTCG TCTGTGTGTT
                                         T
TTAGTTTCAT CACCTGTTAT CTGTGTTTGC TGAGGAGAGT GGAACAGAAG     55600
GGGTGGAGTT TTGTATAAAT AAAGTTTCTT TGTCTCTTTA TTTTTTATGT
ATTAACCAAA CATACCTCCA GACACTGCTG TGAGTGCTGT GTCTCTGTTA     55700
ACTCCTGGAA TTCACCCATC CAGAGGAACC AGGATGCAAG AGGTTAAGAA
```

FIGURE 1J

```
ACTTGCCGTC TGGGTTTGGG TTCCCCATAC AAGGATTCAA ATAGTTGATT          55800
          A
TAGGAAGTAA TCCCGGGAAA CCCTGCTAAG GTAGTGGGGA ACTGAGGCAG
GGAAGGACAC AAACCAAGAA AGTGTTACCT GAAAGGGGTC CAGATGCAGA          55900
CCCCAAAAGA GGGTTCTTGA ATCTCATGCA AGAAAGAATT CAGAGCGAGT
CCATAGAGTC AGTGAAAGCA AGTTAATGAG GAAAGTAAAG GAATAAAAGA          56000
ATGGCTACTC CGTAGACAGA GCAGCCCTGA GGGTTGCTGG CTGCCTATTT
TTATGGTTAT TGATTAATTA TATTCCAAAC AAGGGGTGGA TTATTATGCC          56100
TCCCTTTTAG ACCATATAGG GTAACTTCCT GATGTTGCCA TGGCATTTGT
AAACTGTCAT GGCGCTGTTG GGAGTGTAGC AGTGAGGACA ACCAGAGGTC          56200
ACTCTTGTTG CCATCTTGGT TTTGGTGGGT TAGAGCCATC TTCTTTACTG
CAACCTGTTT TATCAGCAAG GTCTTTATGA CTTGTATCGG TGACGACCTC          56300
CTGTCTCATT CTATGACTAA GAATGCCCTA ACCTCCCAGG AATGCAGCCC
AGTAAGTCTC AGCCTCATTT TACCCAGCCC CTCTTCAAAG CTCCAGTTTA          56400
AATAAACCTC TGACAAAAGG GTGAGTTATT CAACAGATTA CCAGCATGAG
TAACTGATGC TTACCTGCCG GGGATCTCTG GAAGACCATG CATGGCACAT          56500
GCCCAGTTAT GCCTGCAAAG GAGAGGGAGC TGGGGTATTT GTCCACCAGC
TCCCATCTGT CATTGGCTGA GAGCTGCTTC CAGGAGCATT AATTCTCCAG          56600
CACTTCCAGC TACTCCAGGA AAAAAAAAAT TCTTCAACTG AGAGTTGGAG
GTGTTGAGAG ACTCTGGCAC ACCAAGAAGA CAGGAACAGG ACACCAACAG          56700
TGGCTGATGA TACACTGCCA AGGTCACACA GCTAGTTAGC AACAGATCTA
TAGTGGAATC CAGACAGTGT CTCCATCACC CAGGCTCTCT GTAGTGATCT          56800
GCGCTTCACA TCCGAGGCAG GCAGAGGGAT GGTGTGGGCC TTAGATGGGA
AGGCTGGGAA CCTGAAGCTC CTATGTCTGT ATCACTTTTG CTTCTCTGAG          56900
TAGCTGCCCT GATTTCACAC TTGAGGGGCT TGGCCATTTT AGATTCCTTC
CTGCTCTAGG AGCCTACATA CTACACTGGA AATGATGGGG AGCTCTCTAC          57000
CTCACATGCA GCCTGATGTT TGTTAGAAAC ACCTCCTTGC GCCAGGCATG
ATGGCTCATG GCTGTAATCC CAGCAATTTG GGAGGCTGAG GCGGGTGTAT          57100
CACTTGAGGT GAGGAGTTCA AGACCAGCCT GGCCAATATG GTGAAACCCT
ATCTCTACCA AAAAATAAAA AATTAGCCGG GTGTGGTGGT GGGTGCCTGT          57200
AATCTCAGCT ACTTGGGAGG CTGAGTTGGT AGAATTGCTT CAACCTGGGA
CGCGGAGGTT GCAGTGAGCT GAGATTGTGC CATTGCACTC CAGCTTGGAT          57300
GACAGAGTGA GACCCTGTCT CAGGAAAAAA AAAAAAAAAC AAAAAAAACC
TTGTTCTAAG CCAAAATCAA TCCCTTTAGC TGCCCAAATC ACACAGTTTA          57400
CAGATGGAGA AACAGTTTTA GAGAGGAAAA GGGACTTGCC CAAAGTCACC
CAGAGAATGG CAGAGCCTGA ACTAGCCTTC TGGACTTCTT GCCTCCAAAA          57500
GCTCTTTATA ATAAAATATA ATTTTAAATA AAAATAGTTA TCTGTTTAGG
GCCAAGCAAT ATGCTAAGTG CCGTCCAGCC ACTGTGTCAT TTACGTCTCC          57600
AAACAGCTCT AGTTGGGAGG CTCAATGATT ATCCCAATTT TACAGATAAG
GAAACAGGTC CAGAGAGGTT GAGGATTAGC CTAGAACCAC ACAGCTAGGA          57700
AATCCTGGAG CCAGGATTTG AACCCGGGTC TGACCTAAGA GCTCCCAGCC
GCCGTGATAT ATCAGCTTAT GTCATCCTGA CACCTACGCA GATGTCGGCT          57800
CGAATCCACT TTGCCTGAGC ATTGTCTCAG AGAAATCTAA TTTAAAAATT
AGGCAGCAAA TAGAAAATAT ATTTGACTGC TAGAGATGCA ATGGGACTGG          57900
GAGCCCAACA AAGGATCTTA GGCAAAGAA ATCCAAGTTG TTGGCCTCAG
CAACTATTAC TGAACTGGCT GGGCTTTGGG AAGCTACAGA GGGATGAGAA          58000
GACCTGGTGG ATCAGGTGGG CCCAACTCAG GCTGGCCCCC ACCCTGCAGG
AAGTAGGAAA AGTCCAGGGT CATAGGCCCA GTGAGATGCC GGCTGCGGGA          58100
GTTTCAGCCT CCGGGGCTGG ACCAGAGGGC AGGAGGGGAC GCCCCTGGGT
AGCAGCGCCA GAGTGGGCTG AGTGGCCTGG GCCCCTGCGG GGGAGCTTTC          58200
AGAGATGTTG ATTTGGGGGT ACTCCCTCAG CCCTGCCTTT ACACAGAATT
TGTGGGGGAT GAGGGGAGGG GGAAGGGGG GAGGAAGGCA GTGAGTGCAT          58300
CTGAATTTTT TTTTTTTTTT TACAAAAAGT GGCTTATTGC ATTTTTCTGA
TTACTCTATC AGCACGTGCA GACCTTTTCC TATTCAGAGA AAGCCTGAAG          58400
ATATAAAGAG GAAAGTGAAG AAAAACCACC GGAAATCCCA TCCCCGCCCC
AGCATCTGGC ACTGTGTGGG CGATCACGAA ATGAGCGCTT GTTTTTGAAG          58500
GCGTAGTATC TCCGTGAACA TCCGGTTGAA CAACCTTTCT GACTTTATTT
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FIGURE 1K

11/15

```
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```

FIGURE 1L

POLYMORPHISMS IN THE CODING SEQUENCE OF IL4Rα

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GCGTCTCCGA CTACATGAGC ATCTCTACTT GCGAGTGGAA GATGAATGGT
CCCACCAATT GCAGCACCGA GCTCCGCCTG TTGTACCAGC TGGTTTTTCT          200
GCTCTCCGAA GCCCACACGT GTATCCCTGA GAACAACGGA GGCGCGGGGT
                       G                    T          A
GCGTGTGCCA CCTGCTCATG GATGACGTGG TCAGTGCGGA TAACTATACA          300
                                                      C
CTGGACCTGT GGGCTGGGCA GCAGCTGCTG TGGAAGGGCT CCTTCAAGCC
CAGCGAGCAT GTGAAACCCA GGGCCCCAGG AAACCTGACA GTTCACACCA          400
ATGTCTCCGA CACTCTGCTG CTGACCTGGA GCAACCCGTA TCCCCCTGAC
AATTACCTGT ATAATCATCT CACCTATGCA GTCAACATTT GGAGTGAAAA          500
CGACCCGGCA GATTTCAGAA TCTATAACGT GACCTACCTA GAACCCTCCC
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TCCGCATCGC AGCCAGCACC CTGAAGTCTG GGATTTCCTA CAGGGCACGG          600
      A
GTGAGGGCCT GGGCTCAGTG CTATAACACC ACCTGGAGTG AGTGGAGCCC
CAGCACCAAG TGGCACAACT CCTACAGGGA GCCCTTCGAG CAGCACCTCC          700
TGCTGGGCGT CAGCGTTTCC TGCATTGTCA TCCTGGCCGT CTGCCTGTTG
TGCTATGTCA GCATCACCAA GATTAAGAAA GAATGGTGGG ATCAGATTCC          800
CAACCCAGCC CGCAGCCGCC TCGTGGCTAT AATAATCCAG GATGCTCAGG
GGTCACAGTG GGAGAAGCGG TCCCGAGGCC AGGAACCAGC CAAGTGCCCA          900
CACTGGAAGA ATTGTCTTAC CAAGCTCTTG CCCTGTTTTC TGGAGCACAA
                                          C
CATGAAAAGG GATGAAGATC CTCACAAGGC TGCCAAAGAG ATGCCTTTCC          1000
AGGGCTCTGG AAAAATCAGCA TGGTGCCCAG TGGAGATCAG CAAGACAGTC
CTCTGGCCAG AGAGCATCAG CGTGGTGCGA TGTGTGGAGT TGTTTGAGGC          1100
CCCGGTGGAG TGTGAGGAGG AGGAGGAGGT AGAGGAAGAA AAAGGGAGCT
TCTGTGCATC GCCTGAGAGC AGCAGGGATG ACTTCCAGGA GGGAAGGGAG          1200
                                                      C
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                                                 T
GGAGAATGGG GGCTTTTGCC AGCAGGACAT GGGGGAGTCA TGCCTTCTTC          1300
                                                 C T       C
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GCACAGAGAC GCCCCTCGTC ATCGCAGGCA ACCCTGCTTA CCGCAGCTTC          1500
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ACTGCTGGCC AGACACCTGG AGGAAGTAGA ACCCGAGATG CCCTGTGTCC          1600
CCCAGCTCTC TGAGCCAACC ACTGTGCCCC AACCTGAGCC AGAAACCTGG
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                      T
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```

FIGURE 2A

```
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AGGTCCTCGC CCCCTACAAC CCCCCTGAGG GCCCCAGACC CCTCTCCAGG          2300
   G
TGGGGTTCCA CTGGAGGCCA GTCTGTGTCC GGCCTCCCTG GCACCCTCGG
GCATCTCAGA GAAGAGTAAA TCCTCATCAT CCTTCCATCC TGCCCCTGGC          2400
                                                     C
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FIGURE 2B

ISOFORMS OF THE IL4Rα PROTEIN

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                                         H
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FIGURE 3

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        Stephens, J. Claiborne
        Duda, Amy
        Windemuth, Andreas

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Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu Trp Lys Met
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12

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Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile Pro Glu Asn Asn Gly
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Gly Ala Gly Cys Val Cys His Leu Leu Met Asp Asp Val Val Ser Ala
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Asp Asn Tyr Thr Leu Asp Leu Trp Ala Gly Gln Gln Leu Leu Trp Lys
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Gly Ser Phe Lys Pro Ser Glu His Val Lys Pro Arg Ala Pro Gly Asn
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Leu Thr Val His Thr Asn Val Ser Asp Thr Leu Leu Leu Thr Trp Ser
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Asn Pro Tyr Pro Pro Asp Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala
145   150   155   160

Val Asn Ile Trp Ser Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn
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Val Thr Tyr Leu Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys
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Ser Gly Ile Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr
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Asn Thr Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser
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Tyr Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser
225   230   235   240

Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile Thr
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Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala Arg Ser
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Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser Gln Trp Glu
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Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro His Trp Lys Asn
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13

Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu His Asn Met Lys Arg
305   310   315   320

Asp Glu Asp Pro His Lys Ala Ala Lys Glu Met Pro Phe Gln Gly Ser
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Gly Lys Ser Ala Trp Cys Pro Val Glu Ile Ser Lys Thr Val Leu Trp
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Pro Glu Ser Ile Ser Val Val Arg Cys Val Glu Leu Phe Glu Ala Pro
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Val Glu Cys Glu Glu Glu Glu Glu Val Glu Glu Glu Lys Gly Ser Phe
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Cys Ala Ser Pro Glu Ser Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu
385   390   395   400

Gly Ile Val Ala Arg Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly
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Glu Glu Asn Gly Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu
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Leu Pro Pro Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe
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Pro Ser Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro
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Leu His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp
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Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro Ala
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Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro Arg Glu
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Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu Val Glu Pro
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Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr Thr Val Pro Gln
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Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg Arg Asn Val Leu Gln
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14

His Gly Ala Ala Ala Ala Pro Val Ser Ala Pro Thr Ser Gly Tyr Gln
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Glu Phe Val His Ala Val Glu Gln Gly Gly Thr Gln Ala Ser Ala Val
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Cys Pro Gly Asp Pro Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly
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Leu Asp Arg Glu Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser
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Ser Ser Pro Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp
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Met Pro Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val
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Asp Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu
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Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln Thr
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Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp Arg Ser
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Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser Pro Gly Gly
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Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu Ala Pro Ser Gly
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Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe His Pro Ala Pro Gly
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Val Gly Pro Thr Tyr Met Arg Val Ser
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/19094

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :530/350; 435/69.1, 71.1, 71.2, 325, 252.3, 254.11, 471, 6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 435/69.1, 71.1, 71.2, 325, 252.3, 254.11, 471, 6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,599,905 A (MOSLEY et al.) 04 February 1997 (04.02.97), see entire document.	1-10, 12-20
A	US 5,356,795 A (LEONARD et al.) 18 October 1994 (18.10.94), see entire document.	1-10, 12-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
		"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 OCTOBER 2000	14 NOV 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	PREMA MERTZ
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II   Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

   Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable
   claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
   of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers
   only those claims for which fees were paid, specifically claims Nos.:
   1-10, 12-20

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
   restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

   ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)*

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C12N 5/10, 15/12, 15/63, 15/64; C07K 14/47, 14/705, 14/715; G01N 33/53, 33/567

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, CAS ONLINE, MEDLINE, CAPLUS
search terms: IL4 receptor alpha polymorphic variant, polynucleotide, genotyping, oligonucleotide, method, screening, assay

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-10, 12, drawn to a polynucleotide encoding a polymorphic variant of IL4R alpha, a recombinant organism, the polymorphic variant of IL4R alpha and a method of screening for drugs targeting the polymorphic variant.

Group II, claim 11, drawn to an antibody to the variant.

Group III, claims 13-16, drawn to a composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in a IL4R alpha gene.

Group IV, claim 17-20, drawn to a method of genotyping IL4R alpha.

Group V, claim 21, drawn to a method of predicting a haplotype pair for the IL4R alpha.

Group VI, claims 22-24, drawn to a method of identifying an association between a trait and at least one genotype or haplotype of the IL4R alpha gene.

Group VII, claims 25-26, drawn to a computer system and a genome anthology for the IL4R alpha gene.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Pursuant to 37 C.F.R. § 1.475 (d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first-recited product, a polynucleotide encoding a polymorphic variant of IL4R alpha, a recombinant organism, the polymorphic variant of IL4R alpha and a method of screening for drugs targeting the polymorphic variant. Further pursuant to 37 C.F.R. § 1.475 (d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.